Robotically controlled magnetic capsule endoscopy: new method in the non-invasive diagnosis and screening of upper GI tract disorders

PhD Thesis

University of Szeged
Doctoral School of Theoretic Medicine
Head: Prof. Ferenc Bari, PhD, DSc, full professor, department head
Gastroenterology Subprogram
Head: Prof. László Czakó, MD, PhD, full professor

PhD candidate:
Milán Szalai, MD
Endo-Kapszula Private Medical Centre, Székesfehérvár

Supervisor:
László Madácsy, MD, PhD, university private professor
Endo-Kapszula Private Medical Centre, Székesfehérvár
and
Semmelweis University Department of Surgery, Transplantation and Gastroenterology

Szeged, 2023

List of full papers and abstracts related to the subject of the thesis

I. Szalai M., Helle K., Lovász B. D., Finta Á., Rosztóczy A., Oczella L., Madácsy L., First prospective European study for the feasibility and safety of magnetically controlled capsule endoscopy in gastric mucosal abnormalities WORLD JOURNAL OF GASTROENTEROLOGY 28: 20 pp. 2227-2242., 16 p. (2022) Q1 IF: 5.742 **

II. Szalai M., Schmiedt P., Oczella L., Zsobrák K., Lovász B., Dubravcsik Zs., Madácsy L., Robotically controlled magnetic capsule endoscopy – could it replace diagnostic endoscopy in the near future? CENTRAL EUROPEAN JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY 5: 3 pp. 109-113., 4 p. (2019).

III. Finta A.; Helle K.; Szalai M.; Madacsy L. Use of Magnetically Controlled Capsule Endoscopy by Remote-Control During Pandemic ENDOSCOPY 54: S 01 pp. 261-261., 1 p. (2022) Abstract.

IV. Finta A; Szalai M; Lovasz BD; Helle K; Olle G; Rosztoczy A; Madacsy L Magnetically Controlled Capsule Endoscopy (MCCE) Improves Distal Esophageal Mucosal And Circumferential Z-Line Visibility ENDOSCOPY 53: S 01 pp. 129-129., 1 p. (2021) Abstract.

V. Finta A; Lovász BD; Szalai M; Oczella L; Dubravcsik Zs; Madácsy L Our New Experiences with a Roboticcally Controlled Magnetic Capsule Endoscopy System to Evaluate Esophageal and Gastric Disoders in Patients Referred For Small Bowel Capsule Endoscopy ENDOSCOPY 53: S 01 pp. 97-97., 1 p. (2020) Abstract

VI. Szalai M, Oczella L, Lovasz BD, Madacsy L. Surface mapping in plastic gastric model assisted by a robotic autoscan program with a new magnetically controlled gastric capsule endoscopy system compared to manual controlling. United European Gastroenterol J. 2018:415–A415.

VII. Schmiedt P, Szalai M, Oczella L, Zsobrak K, Lovasz BD, Dubravcsik Z, Madacsy L. A new preparation method for improving gastric mucosal visibility and cleanliness during magnetically assisted capsule endoscopy: A prospective study. Endoscopy. 2019;51:S7

VIII. Madacsy L.A., Lovasz B.D., Zsobrak K., Szalai M., Oczella L. Feasibility and safety of robotically controlled magnetic capsule endoscopy in the visualization of upper gastrointestinal tract October 2018 Conference: United European Gastroenterology Week (UEGW), 2018, Vienna

IX. Lovasz B., Finta A., Szalai M., Helle K., Oczella L., Rosztoczy A., Madacsy L. Results with magnetically controlled capsule endoscopy combined with real-time AI-lesion detection in patients with uninvestigated dyspepsia: a prospective study Central

European Journal of Gastroenterology and Hepatology Volume 8, Supplementum 1 / June 2022 pp 89-90 Abstract

List of full papers and abstracts not related to the subject of the thesis

I. Lovász B.D.; Szalai M; Oczella L.; Finta Á.; Dubravcsik Zs; Madácsy L. Improved adenoma detection with linked color imaging technology compared to white-light colonoscopy SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY 55: 7 pp. 877-883., 7 p. (2020) Q2 IF: 2.423 3.

II. Szalai M; Bajor J; Gyökeres T.; Madácsy L. Use of artificial intelligence in gastroenterology and endoscopy – review and our first clinical experiences CENTRAL EUROPEAN JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY: 1 pp. 2-9., 8 p. (2020) DOI: 10.33570/CEUJGH.6.1.2

III. Kiss E.; Lovász B. D.; Szalai M.; Madácsy L. The impact of quality indicators in endoscopy Guthealth: 1 pp. 14-15., 2 p. (2020)

IV. Bajor J., Dubravcsik Zs.; Hritz I.; Szalai M.; Szepes Z.; Madácsy L.; Czakó L.; Demeter P.; Gyökeres T., Herszényi L. et al. Novelties in the endoscopy of the gastrointestinal tract CENTRAL EUROPEAN JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY 5: 2 pp. 79-87., 9 p. (2019)

V. Szalai M.; Kullmann T., Durcsán H., Regőczi H.; Kiss Gy., Rácz I. [Hemospray: a novel therapeutic option in the management of acute upper gastrointestinal bleeding] ORVOSI HETILAP 156: 13 pp. 528-531., 4 p. (2015) Q3, IF: 0,291

VI. Rácz I; Szalai M.; Kovács V.; Regőczi H.; Kiss Gy.; Kiss Gy., Horváth Z. Mucosal healing effect of mesalazine granules in naproxen-induced small bowel enteropathy WORLD JOURNAL OF GASTROENTEROLOGY 19: 6 pp. 889-896., 8 p. (2013) Q2 IF: 2.433

VII. Rácz I.; Szalai M.; Dancs N.; Kárász T.; Szabó A.; Csöndes M.; Horváthy Z. Pantoprazole before Endoscopy in Patients with Gastroduodenal Ulcer Bleeding: Does the Duration of Infusion and Ulcer Location Influence the Effects? GASTROENTEROLOGY RESEARCH & PRACTICE 2012 Paper: 561207, 7 p. (2012) Q2 IF: 1.615

Number of full publications: 9

Cumulative impact factor of papers 6.762 expected impact factor: 5.742, all: 12.504

1. TABLE OF CONTENTS

.

4. SUMMARY

4.1. BACKGROUND AND AIMS

Capsule endoscopy enabled non-invasive visualisation of the entire small intestine, hardly explorable by conventional diagnostic techniques. Today, capsule endoscopy has become an integral part of the diagnostic routine of small intestinal disorders in internal medicine and gastroenterology, the gold-standard and first-line investigation procedure in small bowel pathologies. Capsule endoscopes currently used in clinical practice are unable to change their speed, direction or position or stay at a given site. Today, the best answer to these technological challenges is provided by the Ankon NaviCam robotically controlled magnetic capsule locomotion system, the prototype of which was first presented in 2012. The system generates an adjustable magnetic field outside the body with a maximum strength of 200 mT, which allows precise, controlled movements in three spatial directions. The system is capable of real-time digital transmission of images to the operating system. These properties make the Ankon NaviCam system suitable for precise manual guidance of the capsule endoscope in the body. In Europe, robotically controlled MCCE apparatuses are currently available at two sites (Sheffield, UK and Székesfehérvár, Hungary), both NaviCam systems developed by Ankon Ltd.

The aim of the study includes: establishing a preparation methodology in the stomach, defining and presenting patient positions and standard examination technique, evaluating the possibility of transpyloric transit by magnetic control, assessment of the safety and potential complications of the methodology, discussing the diagnostic yield, efficacy, safety of MCCE; comparing results obtained with MCCE and conventional gastroscopy, respectively, in a selected patient population.

4.2. METHODS

The MCCE system used in our study (Ankon Technologies Co. Ltd.) includes a special static magnet with robotic and manual guidance, a movable examination table, and a computer workstation with ESNavi software controlling the magnetic system while allowing inspection of the images and evaluation of the findings. The system is capable of real-time transmission of images and signals between the capsule endoscope and the control station allowing the physician or a trained health professional to carry out capsule endoscopy in the stomach. By modifying the magnetic vectors and axes using a computer-based software, these robotic systems can automatically run the gastric mucosa mapping, even without a physician's direct

intervention. There are separate algorithms for exploring the fundus, cardiac region, corpus and antrum. Contraindications for MCCE are the same as those for conventional capsule endoscopy and magnetic resonance imaging (MRI). To achieve optimal gastric mucosal visualisation and standardisation of the MCCE protocol in the stomach, we defined nine different stations with different patient positions. Changing the patient's position from the left lateral decubitus to the supine and right lateral position is necessary to combine gravity and magnetic force, which improves capsule manoeuvring.

4.3. RESULTS

MCCE has been shown to be a feasible and effective method for exploring the gastric and entire small bowel mucosa in 93.7% of tested patients. The average total procedure time was 5 h 48 min 35 s (5 h 46 min 37 s / 5 h 50 min 18 s). Helicobacter pylori positivity was confirmed by urea breath tests in 32.7% of patients tested for small bowel indications. No significant correlation was found between the Helicobacter status and the type (proximal or antral), distribution (diffuse or focal), or severity (minimal or active erosive) of gastritis. MCCE is a safe and non-invasive procedure. Mild complications occurred in 4 patients (oesophageal and small bowel retention in two patients each); each case could be resolved endoscopically or by conservative medication. Severe complications requiring hospitalisation did not occur. To improve visibility, we developed a unique preparation procedure with a combination of bicarbonate, Pronase B and simethicone combined with a patient body rotation technique for better distribution in the stomach. Cleanliness and visibility of the gastric mucosa with these technics can be improved significantly. In MCCEs conducted according to the modified oesophageal protocol first published by our team, the cardiac region and the Z-line could be partially and fully visualised in 90% and 73% of the patients, respectively. Active magnetic guidance of the capsule allowed transpyloric transit in 30 min in 41.9% of the cases, with the Vater papilla visualised in 30%. The diagnostic yield for detecting any abnormalities in the stomach and the small bowel with MCCE for small intestinal indication was 81.8%: 68.6% for minor and 13.3% for major pathologies. 25.8% of the abnormalities were found in the small bowel and 74.2% in the stomach. The diagnostic yield for stomach and small bowel pathologies was 4.9% and 8.4%- for major pathologies and 55.9% and 12.7%, respectively, for minor pathologies. MCCE and gastroscopy findings were compared in 31 patients who underwent both procedures on the same day. The results demonstrated high concordance and similar effectiveness in the detection of focal and diffuse lesions.

4.4 CONCLUSIONS

Combined gastric and small bowel MCCE is recommended in patients referred for small bowel capsule endoscopy (IBD, OGIB and iron deficiency anaemia), as it significantly increases the diagnostic yield of the capsule procedure. Furthermore, in view of high MCCE accuracy compared to gastroscopy, particularly in focal lesions, gastric MCCE may be considered in patients under the age of 40 with complaints suggesting functional dyspepsia without alarm symptoms in whom gastroscopy is not justified, thus reducing the number of unnecessary and invasive gastroscopic examinations and shortening the waiting list, without risking undetection of significant lesions.

5. INTRODUCTION

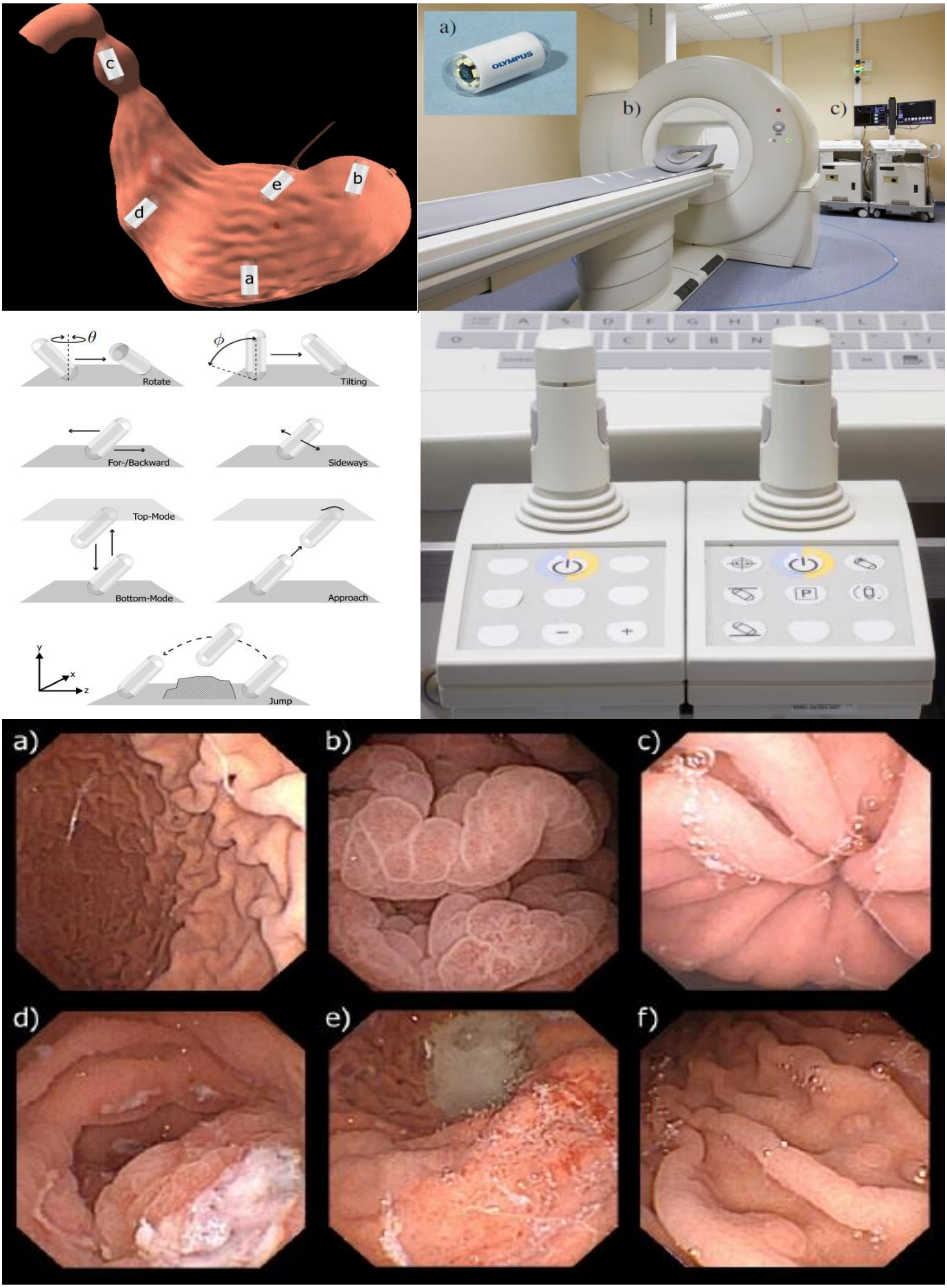
Development of the first capsule endoscopic systems started in the early 1980s when nanotechnology facilitating safe passage of the ingestible capsule endoscope in the gastrointestinal tract became available. Capsule endoscopy was patented and approved by the FDA in 2001 (1, 2). Capsule endoscopy enabled non-invasive mapping of the entire small intestine, hardly explorable by conventional diagnostic techniques. Today, capsule endoscopy has become an integral part of the diagnostic routine of small intestinal disorders in internal medicine and gastroenterology, the gold-standard and first-line investigation procedure in small bowel pathologies (3).

Capsule endoscopy systems consist of four main parts: 1. a single-use ingestible capsule endoscope; 2. a signal recorder placed on the patient’s body, either in contact form similar to a conventional ECG electrode or as a non-contact belt; apart from receiving signals, the areal system is capable of locating the images taken by the capsule within the abdomen; 3. an image recording unit attached to the signal recorder, with a display showing real-time images on more recent models; 4. a workstation for downloading and evaluating the images and reporting the findings (Picture 1). According to current guidelines, small-bowel capsule endoscopy is the diagnostic method of first choice in cases of so-called obscure gastrointestinal bleeding (bleeding of unclear origin), known or suspected. Furthermore, small-bowel endoscopy is indicated in established or suspected Crohn’s disease to assess small-bowel involvement and the extent of inflammatory activity, as well as in coeliac disease, polyposis syndromes affecting the small intestine, and for investigating patients with suspected small intestinal neoplasia (4). Capsule endoscopy today allows high-definition, wide-angle, colour-filter imaging, similar in quality to conventional endoscopy. However, in order to make capsule endoscopy a non-invasive diagnostic alternative to conventional endoscopy in all sections of the gastrointestinal tract, two major problems must be resolved. One is controlled imaging. Camera movement in conventional endoscopy is controlled by means of wheels, allowing the operator to revisit suspicious sites several times and examine them more closely, thus maximising the diagnostic value of the procedure. In contrast, capsule endoscopes currently used in the daily routine drift passively through the gastrointestinal tract, relying on its peristaltic activity for passage. Although diagnostic accuracy can, to some extent, be improved by increasing the image recording frequency and adaptive frame rate (imaging frequency increases with the increased speed of capsule movement), the natural curves and folds in the gastrointestinal tract, the variability of the lumen width, and the uncontrolled drift and spin of the capsule inhibits comparable visibility to that achieved by conventional endoscopy (5, 6). The other major problem observed during capsule endoscopy is capsule retention caused by lack of peristaltic activity (so-called diabetic gastroparesis) or functional stenosis in the gastrointestinal tract leading to temporary or complete capsule blockage. Conventional capsule endoscopes move exclusively by making use of intestinal peristalsis. Capsule endoscopes currently used in clinical practice are unable to change their speed, direction or position or stay at a given site. Capsule robots, however, would be able to move forward or backward or remain in one place, even for longer periods of time. Several capsule robot prototypes capable of active locomotion in the human gastrointestinal (GI) tract have been developed during preliminary research (7). There are two main directions in developing capsule endoscopes with active movement: internal and external. Internal guidance means that the locomotive system (propeller, jet pump, legs) is integrated into the capsule. These systems, however, require a significantly higher amount of energy. The main drawback of internal locomotive systems is that built-in active propelling mechanisms also increase the possibility of error. External guidance involves the use of an external control mechanism for locomotion, e.g. a magnetic control unit or device/moving arm generating a magnetic field. This approach has the exceptional advantage of saving energy as locomotion is realised by creating (and modulating) a magnetic field generated by an external unit and a magnet within the capsule. On the other hand, the locomotion thus achieved is passive and relatively inflexible, and the locomotive potential of the magnetic field is greatly influenced by the distance between the capsule and the external unit. The capsule is externally controlled by the operator using an external control unit, resulting in reduced spatial and temporal accuracy. In view of the considerations discussed above, a technology allowing active locomotion of the capsule endoscope would be a significant step forward, leading to improved diagnostic accuracy. Locomotion of the capsule could - obviously - have several potential long-term benefits, not only in diagnostics but also in therapy (targeted biopsy and treatment, e.g. laser tumour ablation, drug delivery).

Picture 1

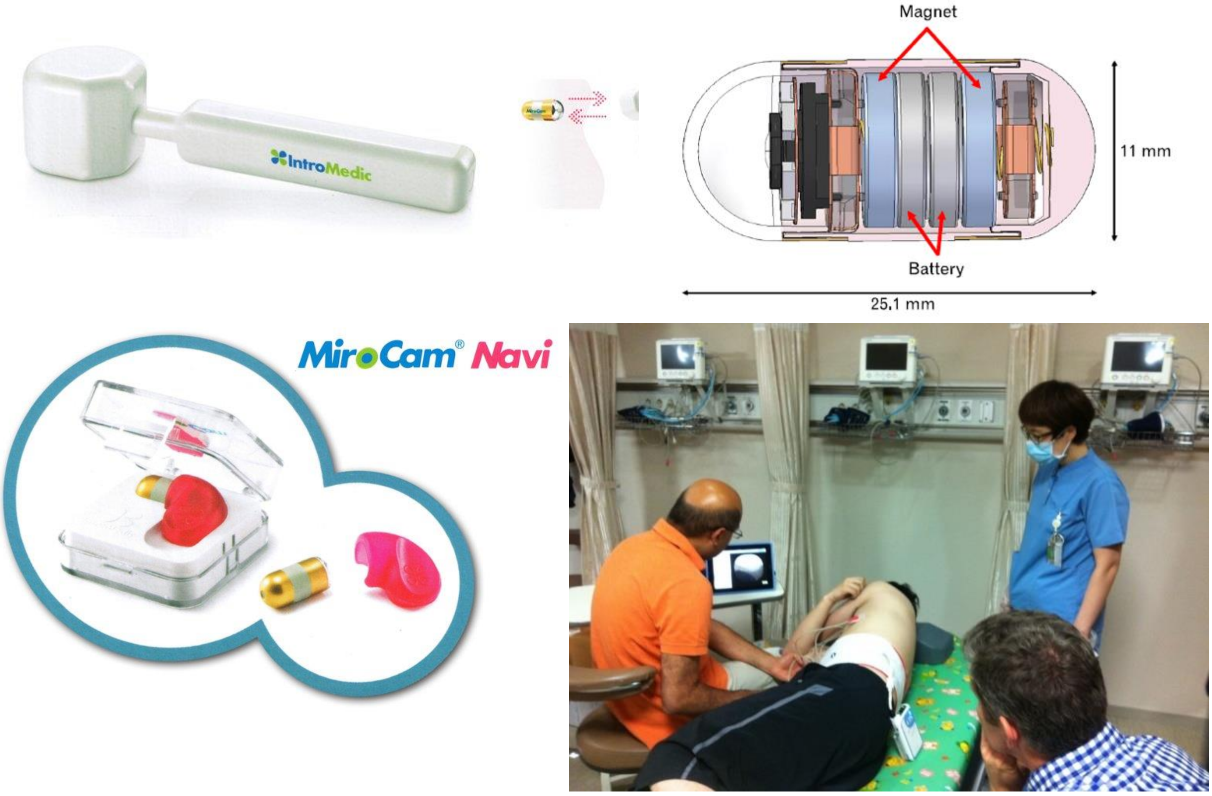
Magnetically controlled capsule endoscopy (MCCE)

It was in 2006 that the idea of magnet-assisted capsule endoscopy was born, and the first prototype was built. The results of the first clinical trial using a modified capsule controlled by a manual magnet were published in 2010. In their first studies, Swain et al. used modified Given colon capsules, which they were able to move in the oesophagus and the stomach (8). Experience drawn from previously conducted *in vitro* experiments made it clear that locomotion and precision of the capsule movement were significantly influenced by the physical properties of the magnetic field created by the external magnetic unit. In 2011, Olympus introduced a capsule endoscope controlled by an external magnetic field to explore the stomach. The capsule was moved using a modified conventional MR apparatus which created a reduced force magnetic field allowing the operator to guide the capsule in any chosen direction within the stomach by means of two joysticks for changing the direction of the magnetic field. In the 53 patients included in their study, the investigators were able to visualise 98%, 96%, 73% and 75% of the antrum, corpus, fundus and cardia, respectively, after filling up the stomach with water (9). In their next trial, capsule endoscopy was performed 24 h after conventional gastroscopy in 61 patients. In order to remove gastric mucus and achieve the required extent of distension, the subjects were made to drink water in two portions. 58.3 % of the pathologies were identified by both methods. Compared to the other modality, 14 abnormalities were missed by capsule endoscopy and 31 by gastroscopy; the diagnostic yield was similar in both modalities (10). However, due to the difficulty of installation and low cost-effectiveness, this technique never became widespread in practice (Picture 2). In 2014, Intromedic developed a navigation (NAVI) magnetic capsule system that could be moved externally with a small hammer-shaped static magnet (Picture 3). Although the technology involving an external magnet that assisted the operator in manually moving the capsule endoscope appeared successful, it never led to a breakthrough as it only allowed sudden and harsh position changes of the capsule. Despite these limitations, in clinical trials using small cohorts, 65-86% of the gastric mucosa could be visualised accurately using external magnetically controlled locomotion after the ingestion of water, and the diagnostic accuracy was similar to that achieved by standard gastroscopy (11). In another trial, using a similar type of NAVI capsule system, capsule endoscopy was performed on the large intestine, where magnetic locomotion directed the capsule from the coecum to the sigmoid colon while a colonoscopy probe was inserted to monitor capsule movements and provide dilation by air blow. Manoeuvrability was deemed good or moderate in 94.23% and 5.77 % of the cases, respectively. Six pathologies were identified by the capsule modality and all were confirmed by colonoscopy (12). In 2018, a British study of magnetic assisted capsule endoscopy (MACE) in patients with iron deficiency anaemia using a magnetic hammer in a similar way tested the suitability of the MACE system for the diagnostic examination of the stomach and the entire small intestine in one sitting after a negative colonoscopy. The procedure using the Intromedic NAVI system was performed on 49 patients. The investigators found that significantly more pathologies could be detected by MACE than by gastroscopy alone, and no significant difference in diagnostic accuracy was found when examining the upper gastrointestinal tract only. Iron deficiency was explained by abnormalities in the small intestine in 17 patients; in 15 patients, however, pathologies in the stomach, identified by both conventional and capsule endoscopy, also contributed to the condition. Combined examination of the upper gastrointestinal tract detected more pathologies than gastroscopy alone, the diagnostic yield was higher and tolerability was better (13). Precise locomotion of the magnetic capsule inside the gastrointestinal tract by manual control is not possible due to the variable density of tissues and the variable distance of the capsule from the external magnet. Moreover, the exact spatial location of the capsule, its relation to the surrounding organs, or the ante- / retrograde orientation cannot be judged accurately. Therefore, alongside the magnetic capsule, a robotically controlled external guiding mechanism capable of considering and calculating the above factors and allowing the operator's input (by joystick movements forward, backwards, upward, downward and sideways) to be executed is needed. Robotic control and magnetic assisted free-hand control were compared in an *ex vivo* study in 2010. Robotic control was found to be successful in achieving the target in 87% of the cases, while manual control was successful in 37%, a finding which confirmed the advantage of robotic control (14). Today, the best answer to these technological challenges seems to be provided by the Ankon NaviCam robotically controlled magnetic capsule locomotion system, the prototype of which was first presented in 2012. The system generates an adjustable magnetic field outside the body with a maximum strength of 200 mT, which allows precise, controlled movements in three spatial directions. During the procedure, the operator guides the magnetic capsule by two joysticks in any chosen spatial direction or along its axis; therefore, he/she can rotate or tilt it. The system is capable of real-time digital transmission of images to the operating system. At the same time, it is continuously monitoring the actual spatial location of the camera and can locate the capsule inside the body at any time by obtaining information from the gyroscope (3D motion detector) and transmitter built into the capsule. These properties make the Ankon NaviCam system suitable for precise manual guidance of the capsule endoscope in the body. The NaviCam system consists of a magnetic capsule endoscope 28 x 12 mm in size, an external guiding magnet, a data recorder, and a computer workstation (Picture 4) with an appropriate software for real-time monitoring and capsule guidance. The capsule can be moved along five different axes with the controlling magnet: two rotational and three 3D spaces. Precise magnetic control is achieved by positioning the examination table, modifying the position of the spherical magnet axis along the 3D space, and dynamically adjusting the strength and direction of the vectorial magnetic fields perpendicular to each other. Moreover, the capsule can advance 360° by a rotational automatism in the direction of the capsule's visual axis. These systems can be automatically operated by a robotically controlled computer software without human intervention. The examination is completely non-invasive and safe, capsule retention being the only complication. Contraindications for MCCE are the same as for conventional capsule endoscopy and MRI. By preprogramming instruction sequences (script) into the computing control unit to explore the stomach from the fundus to the antrum, we created a reproducible examination procedure for mapping the complete inner mucosal lining of the stomach, which lowered the variability among investigators. If the examining physician notices significant pathology, he/she can intervene and move the examination to manual control and revisit the abnormality, increasing the number of images taken of the lesion and optimising the diagnostic accuracy of the test. NaviCam was the first magnetically controlled capsule system that enabled bidirectional data transmission and robotic control. The pictures taken by the magnetic capsule (at a rate of 1-6 fps) and its spatial orientation with continuously monitored energy levels are transmitted via the recording vest to the database and display of the computing unit. At the console, the operator can not only control capsule camera movement but may also modify real-time image capturing speed and brightness and can turn the camera on or off (15, 16). In recent years, publications on magnetic assisted capsule endoscopy of the stomach have been dominated by discussions of robotically controlled systems. A review published in 2021 found robotically controlled capsule endoscopy similar to gastroscopy in terms of diagnostic accuracy, while the former had the advantage of greater safety, better tolerability, avoidance of sedation, and a lower risk for infection transmission. It is, however, unsuitable for treatment or biopsy (17). A meta-analysis published in 2021 reviewed studies in which MCCE systems were compared with gastroscopy. The analysis included 7 clinical trials in a total of 916 patients with a total of 745 gastric pathologies identified. Overall sensitivity was 87% distributed as follows: gastric ulcer 82%, gastric polyp 82%, erosion 95%. The duration of the gastric examination was 21.92±8.87 min (18). MCCE was approved by the Chinese Food and Drug Administration for the following diagnostic indications: (1) as an alternative diagnostic tool for patients who refuse to undergo gastroscopy; (2) screening for gastric diseases; (3) screening for gastric cancer; (4) examination of inflammations in the stomach; (5) follow-up for diseases like gastric varices, gastric ulcer, atrophic gastritis, and polyps after surgical or endoscopic removal (19). Earlier and currently available MCCE systems were summarised in a review published in 2021(Table 1) (15). In Europe, robotically controlled MCCE apparatuses are currently available at two sites (Sheffield, UK and Székesfehérvár, Hungary), both NaviCam systems developed by Ankon Ltd.



c
e
b
d
a
a)
OLYMPUS
b)
c)
Rotate
Tilting
For-/Backward
Sideways
Top-Mode
Bottom-Mode
Approach
Jump
a)
b)
c)
d)
e)
f)

Picture 2



Picture 3

Picture 4

Manufacturer	*Given Imaging*	*Intromedic MicroCam - Navi*	*Olympus & Siemens*	*Ankon MCCG-1*	*Ankon MCCG-2*	*JIFU SMCE*	*Jinshan FAMCE*
Launch year	2010	2015	2010	2012	2020	2019	2021
Control	Manual	Manual	MRI guided	Robot controlled	Robot controlled	Robot controlled	Robot controlled
Maximum magnetic field	272 g/cm^2	341 mT	100 mT	200 mT	200 mT	200+50 mT	_
Capsule size	11x31 mm	11x24 mm	11x31 mm	12x28 mm	11.6x 26.8 mm	12x27 mm	_
Capsule weight	7 g	4.2 g	_	5 g	5 g	2.7 g	_
Camera	1	1	2	1	1	1	1
Resolution	256x256	320x320	512x512	480x480	720x720	480x480	512x512
Imaging frequency	4 fps	3 fps	4 fps	2 fps	Adaptive 8 fps	4 fps	Adaptive 2-8 fps
Field of view	156°	175°	>145°	140°	150°	136°	160°
Field depth	0-30 mm	0-30 mm	>20 mm	0-30 mm	0-30 mm	0-50 mm	0-50 mm
Battery life	10 h	8 h	_	>8 h	>12 h	30-40 min	9 h

Table 1. Comparison of different MCCE systems

6. AIMS

6.1 Evaluation of the safety and feasibility of magnetically controlled capsule endoscopy (MCCE) in the examination of the entire upper gastrointestinal tract including the oesophagus, the stomach and the small bowel

Compared to earlier passive locomotion, external magnetic guidance of the capsule endoscope allowed a more precise visualisation of the stomach by combining manual and automated control. However, the cleanliness of the area to be examined is essential, as in any endoscopic exploration. Objectives of the study include: establishing a preparation methodology to facilitate better mucosal visualisation in the stomach and, furthermore, defining and presenting patient positions and standard examination techniques to be used in MCCE; evaluation of the possibility of transpyloric transit by magnetic control and presentation of related results; and finally, assessment of the safety and potential complications of the methodology, as well as the feasibility of the complete exploration of the stomach and the small intestine.

6.2 EVALUATION OF THE DIAGNOSTIC YIELD AND SAFETY OF MAGNETICALLY CONTROLLED CAPSULE ENDOSCOPY (MCCE)

MCCE, capable of guiding the capsule endoscope in the stomach, may become an alternative to gold-standard gastroscopy in special patient populations, primarily in screening for upper gastrointestinal tract disorders, or may function as a non-invasive procedure prior to gastroscopy. MCCE is non-invasive, does not require sedation, and is better tolerated by patients, as shown in previous studies. In this paper, which is the first to evaluate MCCE in a European patient population, our aim is to present the results obtained in patients undergoing MCCE for gastric or small bowel indications; to discuss the diagnostic yield, efficacy and safety of MCCE; and to compare the results obtained with MCCE and conventional gastroscopy, respectively, in a selected patient population.

7. METHODS

7.1 Technical methods

The MCCE system used in our study (Ankon Technologies Co. Ltd.) includes a special static magnet with robotic and manual guidance, a movable examination table, and a computer workstation with ESNavi software controlling the magnetic system while allowing inspection of the images and evaluation of the findings (Picture 5). The capsule endoscope sizes 26.8 x 11.6 mm, weighs 4.8 g, and has a permanent spherical magnet inside. The operator can adjust the frequency of captured pictures from 0.5 to 6 frames per second (fps). Capsule functioning can be stopped temporarily and restarted by the operator remotely from the workstation. The picture resolution is 480 x 480 pixels, and the field of view is 140°. The illumination can be automatically adjusted by an automatic picture-focusing mechanism, which enables the view depth to shift from 0 mm to 60 mm. Depending on the fps, the battery life can be as long as 10 h, which allows combined gastric and small intestinal capsule investigations with the same capsule (Picture 6).

The magnetic robotic C-arm generates an adjustable magnetic field outside the patient’s body with a maximum strength of 0.2 T, which allows precise, controlled movements in three spatial directions. During the procedure, the physician guides the magnetic capsule by two joysticks: the left one induces rotational movements while the right makes the magnetic head move forward/backwards, up/down, left/right. This way, the capsule can be guided in any chosen spatial direction or along its axis and therefore, can be rotated or tilted. By increasing or decreasing the distance from the magnetic field, the capsule can be made to swim, float or sink in the gastric fluid. By pressing the button on top of the left joystick, the capsule can be moved stepwise in a worm-like movement by a preprogrammed algorithm allowing the operator to guide the capsule in the required direction. A gyroscope helps follow the tilt angle and viewing direction of the capsule on the control panel. Precise implementation of the 45° tilt angle and 360° rotation is ensured by the use of preprogrammed buttons.

The system also includes a capsule locator that activates the capsule by infrared light prior to the patient swallowing it and is able to detect the capsule in the body, thus can be used to check the elimination of the capsule (Picture 7). By analysing the movement of the magnetic capsule, the magnetic arm can locate the capsule in the body and automatically positions itself over it, facilitating a stronger magnetic connection and precise guidance.

The system is capable of real-time transmission of images and signals between the capsule endoscope and the control station allowing the physician or a trained health professional to carry out capsule endoscopy in the stomach. As with other capsule systems, a data recorder capable of receiving signals and recording images is attached to the patient's body prior to the examination. The images taken by the capsule are transmitted to the recorder by means of wireless radiofrequency transmission. The numerous special receiving aerials located within the recording vest, insensitive to the magnetic field, enable the localisation of the image within the abdomen (Picture 8). Nine individual frequencies are available for signal transmission, meaning that several examinations may be performed in one space simultaneously, and the procedures may be modified before and during the examinations. A USB connection between the data recorder and the workstation allows real-time inspection of the images and evaluation of the information of the gyroscope.

By modifying the magnetic vectors and axes using a computer-based software, these robotic systems can automatically run the gastric mucosa mapping, even without a physician's direct intervention. There are separate algorithms for the exploration of the fundus, cardiac region, corpus and antrum. For safe use, the lowest point of the robotic arm can be pre-fixed, thus preventing the patient from being squeezed by the apparatus and allowing optimal positioning of the capsule and the magnetic arm in patients of different physiques.

Picture 5. Robotic C-arm, examination table and computer workstation with the control desk

Picture 6. Magnetic capsule endoscope

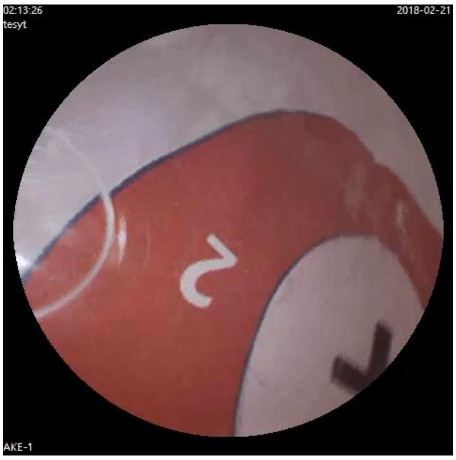
Picture 7. Manual capsule locator and activator

Picture 8. Data recording vest and belt

7.2 Validation of the method

In the learning phase of the application, an in vitro study was designed to compare manual and automated manoeuvring. In the test, 12 different coloured disks numbered by quadrants were attached to the outside of a transparent plastic stomach model of authentic anatomical size fully filled with water: one each to the anterior and posterior walls of the fundus, corpus, antrum, cardia, pylorus and angulus, and three to the large curvature (Picture 9). To compare preprogrammed automated exploration and free-hand control, five automated tests each were run on a small to medium-sized stomach and a medium to large stomach, then two tests were performed by trainee endoscope operators after previous training, applying free-hand control. The percentage ratio of disks in the visual field was used to compare mucosal visualisation. The automated modalities were able to visualise 97.5% and 100% of the disks in all four quadrants with the small to medium-sized and the medium to large stomach protocols, respectively. Trainee operators could visualise 76% of the disks for the first time and 85.4% for the second during a period of time identical to that of the automated algorithm. The average time needed to explore the entire stomach was 749 s in manual mode and 390 s with the longer automated protocol (Picture 10) (20).

Picture 9. Plastic stomach model with the attached disks



Picture 10. Capsule endoscopic image of a disk

7.3 Examination procedure

Contraindications for MCCE are the same as those for conventional capsule endoscopy and magnetic resonance imaging (MRI). Patients with previous abdominal surgery associated with interruption of intestinal continuity; previous capsule retention; implanted MRI-incompatible electronic devices (e.g. defibrillators and pacemakers), or magnetisable non-removable metal foreign bodies; who were not competent or refused to sign the informed consent form; who were under 18 or above 70 years; and those who were pregnant were excluded from the study. A patency capsule test was first performed in patients with relative contraindications, including known or suspected GI obstruction.

In accordance with SBCE guidelines, the patients followed a liquid diet and consumed 2 l of water with two sacks of polyethylene glycol (PEG) the day before the examination. On the day of the examination, first, a Helicobacter pylori urea breath test (UBT) was performed, if applicable, while the patient was in a fasting condition.

Unlike conventional small bowel capsule endoscopy, capsule exploration of the stomach requires appropriate cleanliness and distension of the stomach for optimal mucosal visibility. Based on earlier publications and methodologies used for improving the cleanliness of the stomach in conventional endoscopy, we performed a prospective study involving 60 patients. Thirty patients received our new gastric preparation protocol (Group A: 46.4 years; 50% female), and another 30 patients without special gastric preparation served as controls (Group B: 47.1 years; 33.3% female). The same preparation protocol was used the day before the test (24 hours liquid diet, two doses of PEG). Group A received 200 mg simethicone, 40 mg Pronase B, and 1 mg sodium bicarbonate 40, 30 and 20 minutes, respectively, before magnetically assisted capsule endoscopy. Then the patients were asked to lie down and were rotated every 5 minutes in 90 degrees increments around their axis to facilitate even distribution of the liquid on the gastric mucosa. Patients in Group B had 200 mg simethicone dissolved in 2 dl water before the examination. Finally, 600 ml clear water was given to all patients directly before swallowing the capsule for proper gastric distension. Landmark images of the fundus, body and antrum, one of each for each patient, were analysed with a self-developed software, which calculated the ratio of clean and covered surfaces of the gastric mucosa. The average ratio of covered areas was 7.26% and 12.32% (fundus), 3.36% and 9.22% (body), and 0.31% and 6.14% (antrum) in group A vs B, respectively. The differences were statistically significant in all three regions (p = 0.0053, 0.0012 and 0.0321 in the body, antrum and fundus, respectively) (21).

After the complete mapping of the gastric mucosal surface, active transpyloric propulsion of the capsule was attempted in all patients with the help of the external magnetic field. If neither active nor passive transpyloric passage was successful within 60 min, 10 mg intravenous metoclopramide was administered.

7.4. Examination of the oesophagus, stomach and duodenum

To achieve optimal gastric mucosal visualisation and standardisation of the MCCE protocol in the stomach, we defined nine different stations with different patient positions. Changing the patient's position from the left lateral decubitus to the supine and right lateral position is necessary to combine gravity and magnetic force, which improves capsule manoeuvring.

After the patient has swallowed the capsule, the examination is started in the left lateral decubitus position (Picture 11):

I. Visualisation of the distal section of the oesophagus and the cardia

The patients swallow the capsule with a minimal amount of water lying on their left side, leaning on their elbows in a half-slanted position under the magnetic arm, which is behind their thoracic spine. This way, the magnetic capsule can temporarily be maintained at the height of the cardia, allowing visualisation of the distal section of the oesophagus, the cardia, and the Z-line. When the capsule has passed through the upper oesophageal sphincter with the help of a sip of water, the patients are immediately asked to lie down in a horizontal lateral position, then to slowly turn on their back while the magnet is guided over the sternum thus holding the capsule firmly over the cardia. We have found that in this position the angular break between the distal oesophagus and the cardia is straightened and the total circumference of the Z-line can be drawn into the visual field, with its opening and closure also seen on dry and wet swallows executed the way it is done in manometry. In the meantime, the capsule is passed into the stomach by slowly dragging it with the magnet in the right direction.

II. Visualisation of the gastric fundus and subcardial region with the cardia (posterior J type retroflexion).

After entering the stomach, the capsule is lowered into the large curvature at the body of the stomach. The magnetic ball is held high up at the level of the patient's right shoulder. The capsule camera is maintained in an obliquely upward orientation of 45° and then horizontally rotated to survey the gastric fundus and the cardia.

III. Closer examination of the cardia and fundus (anterior J type retroflexion)

While using the right joystick, the ball magnet is lowered and fitted closely to the patient's right arm. Due to the proximity of the magnetic field, the capsule rises to the anterior wall and small curvature of the stomach. The capsule is then rotated with the camera oriented vertically upward to observe the cardia up close, with the fundus at a distance.

IV. Visualisation of the gastric corpus from the fundus

With the ball magnet in the same position, the capsule camera is rotated and tilted downwards using the left joystick, enabling visualisation of the proximal part of the corpus and the gastric folds at the large curvature from a longitudinal view (Picture 12).

Stations in the supine position

V. Visualisation of the angular incisure

The patients are asked to lie on their backs in a supine position. The capsule is located in the distal area of the gastric corpus and is guided towards the angular region by stepwise magnetic movements, making use of the change in gravity. The magnetic ball is moved over the left upper abdomen (hypochondrium) and then lowered close to the patient's body. At this point, the capsule is raised to the anterior wall of the stomach, allowing thorough examination of the small curvature and the angular incisure as well.

VI. Visualisation of the large curvature from the distal corpus and the angular incisure (U type retroversion)

The magnetic ball is steered over the epigastric area, close to the abdominal wall. Then the capsule camera is oriented upward to explore the anterior wall of the gastric corpus. In this position, the capsule can be turned and rotated (e.g. towards the cardia), enabling visualisation of the distal body of the stomach longitudinally (as in the endoscopic view of U-type retroversion) (Picture 13).

Stations in the right lateral decubitus position

VII. Visualisation of the antral canal

The patients are asked to turn to the right lateral decubitus position. Due to the force of gravity, the capsule sinks and moves spontaneously into the antral canal. The ball magnet is then positioned over the left kidney. The capsule is steered closer to the large curvature with the camera oriented obliquely downward at 45°, which enables observation of the antrum. Then, the antral canal can be examined with the pylorus and the angular incisure visible from the direction of the antrum (Picture 14).

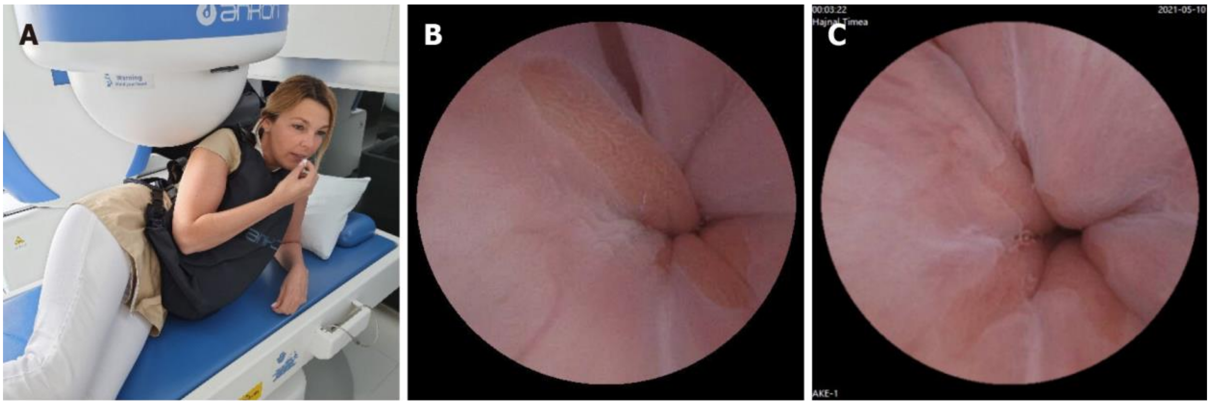
Stations in the supine position

VIII. Prepyloric view and visualisation of the pylorus

After this, the patients are asked to lie on their backs again. The ball magnet is positioned close to the body, over the upper right quadrant of the abdomen (hypochondrium). The capsule camera is guided horizontally and laterally toward the pylorus for closer observation. The magnet position ensures that the capsule remains in the antrum. Using both the right and left joysticks, we move the capsule closer to the pylorus.

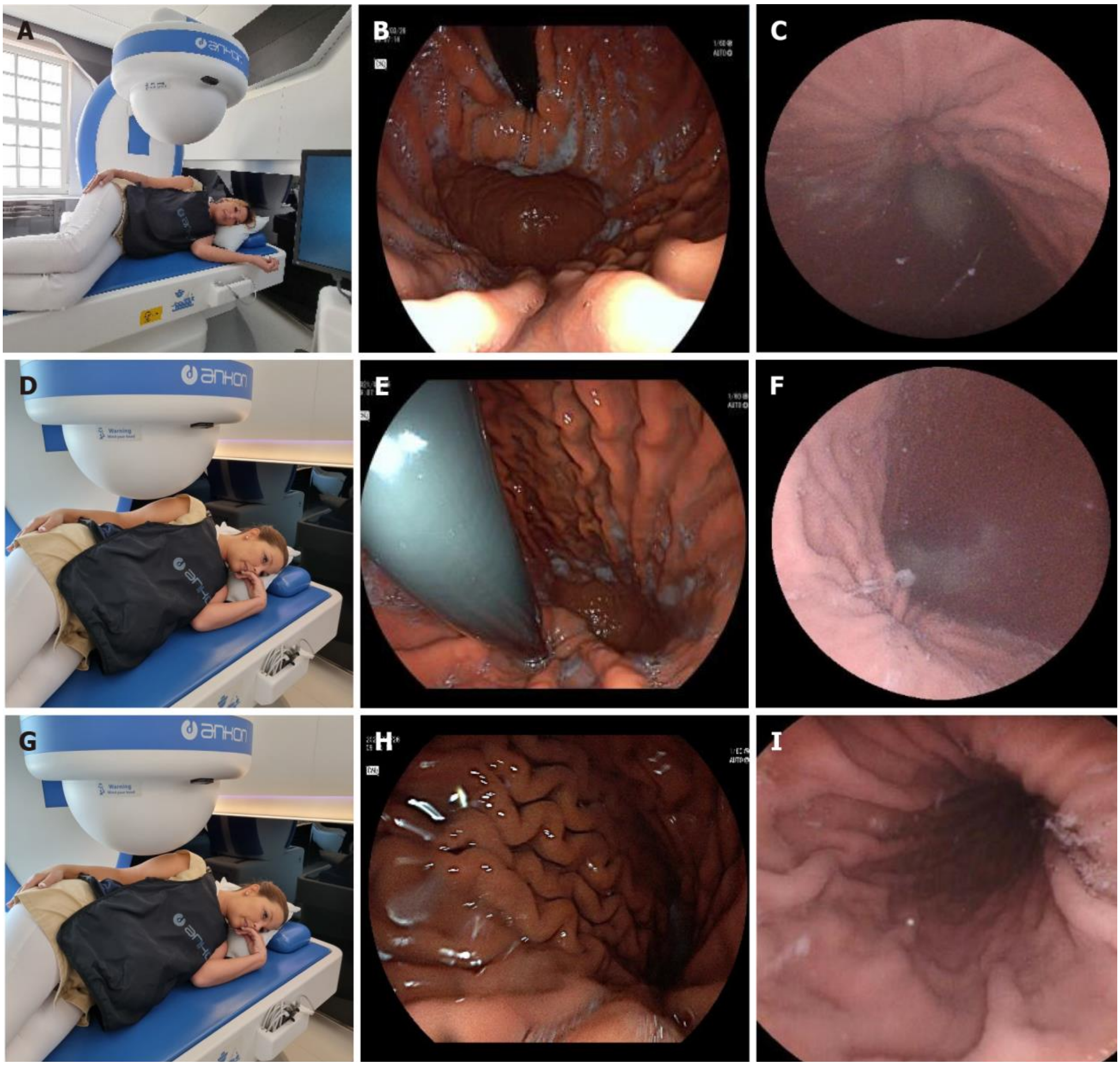
IX. Magnetically controlled transpyloric passage and visualisation of the duodenum

The magnetic ball is placed on the patient's right side at the level of the duodenal bulb. The capsule is then rotated until the camera faces the pylorus. The capsule is dragged close to the pylorus under the guidance of the magnet. When the pylorus opens, peristalsis passes the capsule into the duodenum. After the transpyloric passage, first the duodenal bulb, then the descending and lower horizontal sections of the duodenum are visualised. In the bulbus, the camera is able to visualise the side of the pylorus facing the duodenum and the entire apex bulbi because the capsule here can be rotated and kept in one place. The Vater papilla can be visualised by tilting the capsule camera in cranial and oral directions to facilitate an easier retrograde view, feasible in nearly 30 to 50% of all patients (Picture 15). In Picture 16, capsule stations and camera orientations are shown in a schematic figure.

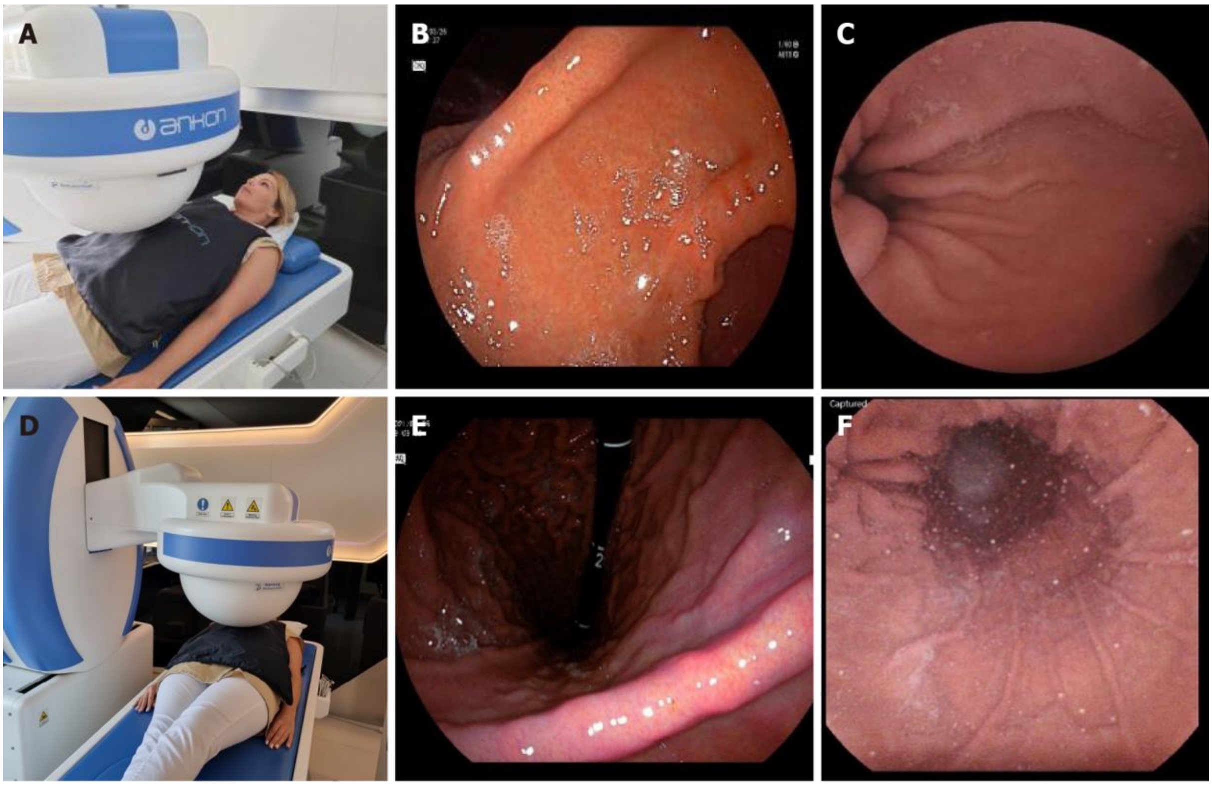


Picture 11. A: The capsule swallowed in the left lateral decubitus position, position of the patient and the magnet; B and C: Pictures of the Z-line by capsule endoscopy (from our

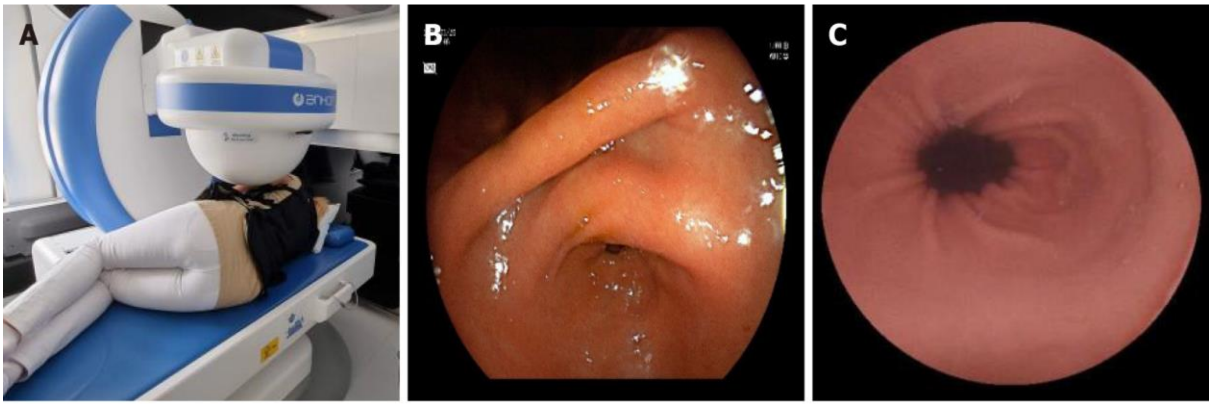
database)



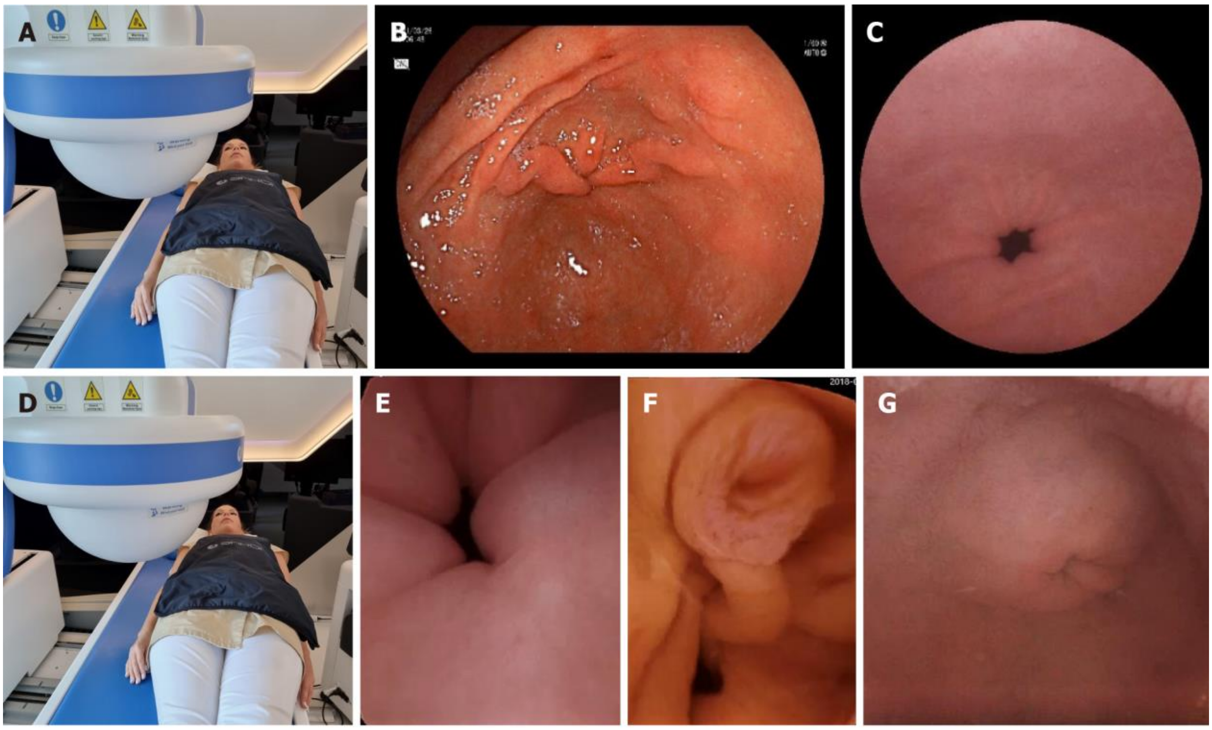
Picture 12. A, D, G: Stations I-III in left lateral positions, position of the patient and the magnet; B, E, H: Gastroscopic pictures corresponding to the positions C, F, I: Capsule endoscopic pictures corresponding to the positions (from our database)



Picture 13. A, D: Stations IV-V in supine position, position of the patient and the magnet; B, E: Gastroscopic pictures corresponding to the positions; C, F: Capsule endoscopic pictures corresponding to the positions (from our database)

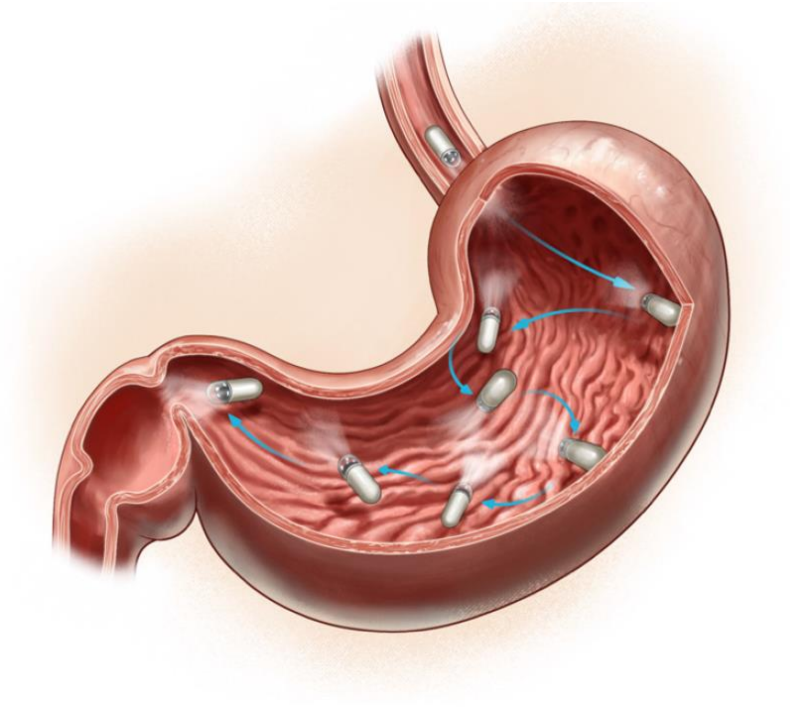


Picture 14. A: Station VI, in right lateral position, position of the patient and the magnet; B: Gastroscopic picture corresponding to the position; C: Capsule endoscopic image corresponding to the position (from our database)



DOI: 10.3748/wjg.v28.i20.2227 **Copyright** © The Author(s) 2022.

Picture 15. A, D: Stations VII-VIII in supine position, position of the patient and the magnet; B: Gastroscopic picture corresponding to the position; C, E: Capsule endoscopic pictures of the antrum and pyloric ring corresponding to the position; F: Capsule endoscopic picture of the Vater papilla; G: Picture of the pylorus from the duodenal bulb (from our database)



Picture16. Different magnetically controlled endoscopic stations and camera orientations for visualisation of the entire gastric mucosa (by Zoltán Tóbiás M.D.)

7.5. Examination of the small intestine:

When the capsule has passed into the small intestine, the patients are asked to drink 1 l of PEG solution, then further amounts of clear liquid. The passage of the capsule in the small intestine is then monitored hourly in real-time visualisation mode. The examination ends when the capsule arrives at the colon or stops functioning due to the low battery. The test is evaluated and the findings are reported after the images have been transloaded from the recording vest onto the analysing station (22).

8. PATIENTS AND METHODS

8.1. Study design

Our study prospectively enrolled all outpatients who were referred for small bowel capsule endoscopy and seen at the Endo-Kapszula Endoscopy Centre, Székesfehérvár, Hungary, between September 2017 and December 2022 who accepted and agreed to our study protocol. These patients were subjected to a combined investigation of the stomach and small bowel with a robotic magnetically controlled capsule (MCCE) system as described in the methodology (NaviCam, Ankon Technologies Co, Ltd, Shanghai, China). This study was approved by the Ethical Committee of the University of Szeged (Registry No. 5/17.04.26) and registered in the ClinicalTrials.gov trial registry (Identifier: NCT03234725). The present study was conducted according to the World Medical Association's Declaration of Helsinki provisions. All patients agreed to undergo MCCE and Helicobacter pylori urea breath tests (UBT) by written informed consent.

8.2. Patients

The first study included 284 patients, 149 of them male (52.5%) and 135 female (47.5%), with a mean age of 44 years. Detailed demographical data are presented in Table 2.

	Total	Male	Female
No. of cases	284	149 (52.5%)	135 (47.5%)
Age (mean ±SD)	44.0 ±13.3	44.0 ±13.3	44.0 ±13.3
BMI	26.5	27.1	25.5

Table 2: Demographical data

The indications for MCCE were the same as those for conventional small bowel endoscopy: iron deficiency anemia, obscure gastrointestinal bleeding (OGIB), suspected or established Crohn's disease, suspected or confirmed coeliac disease, unexplained abdominal pain, suspected small bowel neoplasia, carcinoid syndrome, and small bowel polyposis. The distribution of indications by gender is contained in Table 3 (22).

	ALL CASES	**MALE**	**FEMALE**
OGIB	61 (21.5%)	30 (20.1%)	31 (22.9%)
COELIAC DISEASE	80 (28.2%)	40 (26.8%)	40 (29.7%)
SUSPECTED OR ESTABLISHED CROHN’S DISEASE	47 (16.5%)	31 (20.9%)	16 (11.9%)
UNEXPLAINED ABDOMINAL PAIN	92 (32.4%)	47 (31.5%)	45 (33.3%)
SUSPECTED SMALL BOWEL NEOPLASIA	4 (1.4%)	1 (0.7%)	3 (2.2%)

Table 3: Distribution of indications for MCCE by gender

For the second study, patients with complaints suggesting functional unexplored dyspepsia without alarm symptoms were selected. 270 patients were entered in this study and their dominant complaints included upper abdominal discomfort, ulcer-like upper abdominal pain, nausea, early sense of fullness, and postprandial tightness. All patients were younger than 50 without alarm symptoms, in whom gastroscopy as first choice was not deemed justified, and the patients themselves preferred a non-invasive modality although they had been offered gastroscopy under propofol sedation as an alternative. In this patient cohort, the mean age was 38 years, and the male/female ratio was 108/162. A real-time AI-based focal lesion detecting software was also applied during the examinations. In case MCCE detected severe, potentially erosive gastritis or focal lesions in the area of the cardia, stomach or duodenum associated with

Helicobacter positivity (with the exception of foveolar hyperplastic polyps smaller than 5 mm associated with PPI medication), standard gastroscopy and biopsy were also performed on the same day. The patients in this cohort swallowed the magnetic capsule in left lateral position under magnetic control using the oesophageal protocol. This allowed prolonging the transit time in the oesophagus and focusing on the area around the cardia (23).

9. RESULTS

UBT tests performed prior to MCCE revealed Helicobacter pylori (HP) positivity in 32.7% of the cases (Table 4). No significant association between the HP status and the type (proximal or distal), distribution (diffuse or focal) or severity (minimal or active erosive) of the gastritis visualised on MCCE was found (Table 5).

The mean gastric, small bowel and colon transit times with MCCE were: 47 h 40 min (M/F: 44 h 15 min/51 h 14 min), 3 h 46 min 22 s (M/F: 3 h 52 min 44 s/3 h 38 min 21 s) and 1 h 4 min 34 s (M/F: 1 h 1 min 16 s/1 h 8 min 53 s), respectively. Average total time of MCCE procedure: 5 h 48 min 35 s (M/F: 5 h 46 min 37 s/5 h 50 min 18 s) (Table 6).

The diagnostic yield for detecting any abnormalities in the stomach and the small bowel with MCCE was 81.9%: 68.6% for minor pathologies and 13.3% for major pathologies. 25.8% of the abnormalities were found in the small bowel, and 74.2% were in the stomach. The diagnostic yield for the stomach/small bowel was 4.9%/8.4% for major pathologies and 55.9%/12.7% for minor pathologies (Table 7).

In the stomach, ulcers, polyps and tumours were considered major, while signs of gastritis, multiple small erosions and multiple small fundic gland hyperplastic polyps were minor pathologies. In the small bowel, signs of inflammation or ulcers of Crohn's disease, polyps, tumours, and celiac disease were the major, and non-specific inflammation (hyperaemia or small erosions), diverticula, lymphoid polypoid hyperplasias and angiodysplasias the minor pathologies. The distribution of pathologies detected by MCCE is shown in Table 8. Patients who tested positive in UBT with associated gastric complaints or were found to have gastric pathologies in MCCE were prescribed a HP eradication course in accordance with the guidelines, and the outcome was followed up.

Our team developed a modified oesophageal protocol for MCCE, which significantly improved the visualisation of the oesophageal body and distal oesophageal mucosa compared to earlier conventional capsule ingestion techniques (24). The modified protocol allowed a significant increase both in average transit time in the oesophagus and in the number of images taken by the capsule camera: 82 sec vs 24 sec and 423 vs 120 still images. Furthermore, visibility of the partial and total circumference of the Z-line increased to 90% vs 36% and 76% vs 23%, respectively, compared to the conventional protocol. This means that erosive reflux disease and Barrett's oesophagus could be detected with MCCE if they present in more than two-thirds of the patients using the modified procedure.

The capsule's active magnetic movement through the pylorus was successful in 41.9% of all patients (automated protocol in 56 patients and manual control in 63 patients). In 18 (M/F: 6/12) patients (6.3%), small bowel visualisation with MCCE was incomplete. According to ESGE guidelines, the procedure and the technology are considered acceptable if at least 80% of small bowel examinations are completed successfully. The optimal target value is 95%, very close to the 93.7% rate achieved with combined gastric and small bowel MCCE. There were 13 occurrences of incomplete examinations because of capsule battery depletion. In 3 of these 13 cases, the capsule was depleted within 5 h of operation, suggesting manufacturing error. In the remaining 10 patients, incompletion was due to delayed small intestinal transit; in these cases, the average total examination time was 9 h 12 min 9 s, and from the pylorus to the last image, the average transit time was 8 h 26 min 4 s. The examination was discontinued earlier than planned in 3 cases on the patient's request. If these 3 cases are not considered in the statistics, 96% of the capsule endoscopies performed for small bowel indications in our MCCE study were completed in the stomach as well as the small intestine, which proves that the technology is suitable for exploration of the entire upper gastrointestinal tract.

Complications: In 2 patients due to oesophageal spasm in the mid part of the oesophagus caused the capsule to get stuck; next, the capsule was successfully moved to the stomach with an endoscope in both patients, later, eosinophil oesophagitis was confirmed by biopsy with a conventional endoscope in both patients. In 2 cases, there was capsule retention due to narrowed small bowel lumen (stenosis) caused by Chron's-like ulceration; both cases were resolved with medication and did not require surgery or endoscopic intervention. In 5 patients, the capsule failed to empty from the stomach for as long as 5 hours; in these cases, the capsule was captured in a loop by upper GI endoscopy and passed to the descending duodenum through the pylorus. There were no severe adverse events or complications requiring hospitalisation, or definitive capsule retention, either during the study period or in the total of 1,400 MCCEs performed since then.

	ALL CASES	MALE	FEMALE
NO. OF TESTS PERFORMED	110 (38.7%)	56 (50.9%)	54 (49.1%)
POSITIVE	36 (32.7%)	16 (44.4%)	20 (55.6%)
NEGATIVE	74 (67.3%)	40 (54%)	34 (46 %)

Table 4: Results of Helicobacter pylori C^{13} urea breath tests

	N	**H. PYLORI POSITIVE**	**%**	**H. PYLORI NEGATIVE**	**%**	**KHI^2**	**P VALUE**	
NORMAL	30	7	23	23	77	0.9775	0.3228	NS
MILD PROXIMAL GASTRITIS	19	9	47	10	53	1.529	0.2163	NS
MILD ANTRAL GASTRITIS	19	4	21	15	79	1.0322	0.3096	NS
ACTIVE EROSIVE ANTRAL GASTRITIS	15	6	40	9	60	0.3129	0.5759	NS
PROXIMAL EROSIVE GASTRITIS	22	7	32	15	68	0.0069	0.9339	NS
PANGASTRITIS (PROXIMAL AND ANTRAL)	4	3	75	1	25	0.5	0.4795	NS
TOTAL PATIENTS TESTED FOR H. PYLORI	110	36	33	74	67	-	-	-

Table 5: Correlation of detected pathologies and Helicobacter pylori infection

Transit time	**All cases**	**SD**	**Male**	**Female**
Stomach	0h 47min 40s	0h 43min 29s	0h 44min 15s	0h 51min 14s
Small bowel	3h 46min 22s	2h 1min 24s	3h 52min 46s	3h 38min 21s
Total	5h 47min 35s	1h 50min 49s	5h 46min 37s	5h 50min 18s

Table 6: Mean gastric, small bowel and total transit times in MCCE

DIAGNOSTIC YIELD	MINOR PATHOLOGIES	MAJOR PATHOLOGIES	TOTAL PATHOLOGIES
STOMACH	55,9%	4,9%	
SMALL BOWEL	12,0%	8,4%	
COMPLETE	68.6%	13.3%	81.9%

Table 7: Diagnostic yield of MCCE

	Gastric polyp	Gastric ulcer	Coeliac disease	Crohn's disease	Gastritis	Small intestinal diverticula	AVM	Aspecific small intestinal inflammation
Pathologies	5	9	1	21	159	1	26	9

Table 8: Pathologies detected by MCCE

In the second study, prospectively conducted in patients with symptoms of uninvestigated functional dyspepsia, 28.6% of the patients were HP positive; these patients were prescribed an eradication course following the MCCE examination. Transit times by gender are shown in Table 9. MCCE findings were negative in 40 patients (14.8%), i.e., no diffuse or focal abnormalities were detected either in the distal oesophagus or the stomach. Mild gastritis was found in 102 patients (37.8%). MCCE detected the following pathologies in the oesophagus or the stomach: erosive reflux 73 (27%), suspected short Barrett's metaplasia 6 (2.2%), erosive or active distal gastritis 76 (28.1%), duodeno-gastric biliary reflux 45 (16.7%), foveolar hyperplasia 25 (9.2%), solitary gastric polypoid lesion 9 (3.3%), pangastritis 6 (2.2%), gastric ulcer 5 (1.9%), suspected intestinal metaplasia 4 (1.5%), signs of increased portal pressure and AVM 3 (1.1%), and gastric lesion characteristic of early focal malignancy 1 (0.3%), which was later diagnosed as B-cell lymphoma based on the biopsy taken during gastroscopy (Tables 10 and 11). In cases requiring biopsy, gastroscopy was also performed on the day of the MCCE examination if agreed by the patient. The results of the 31 patients (11.5%) undergoing gastroscopy and MCCE are summarised in Table 12. The results obtained by gastroscopy correlated well with those of MCCE, both for focal and diffuse lesions. Lesions that appeared to be ulcers on enlarged capsule images were found to correspond to larger erosions in gastroscopy, and MCCE more often suggested inflammatory signs of gastritis, which was then sometimes unconfirmed macroscopically by conventional upper panendoscopy. In contrast, there was a microscopically mild, HP negative, reactive inflammation in most of these patients, proved by antral biopsies.

	Stomach	Small bowel	Colon	Total examination time
Mean	0:44:03	3:39:08	1:03:45	5:33:16
Male	0:37:11	3:45:36	1:04:01	5:28:51
Female	0:54:26	3:29:06	1:03:20	5:39:54

Table 9: Transit times by gender

Erosive reflux	**73 (27%)**
GERD LA A	54 (20%)
GERD LA B	9 (3%)
GERD LA-M	10 (3.7%)
GERD LA-C, D	0 (0%)
Suspected Barrett metaplasia	6 (2.2%)

Table 10: Pathologies detected in the oesophagus

Gastritis minor	**102 (37,8%)**
Erosive antral gastritis	76 (28.1%)
Pangastritis	6 (2.2%)
Foveolar hyperplasia	25 (9.2%)
Gastric polyp	9 (3.3%)
Ulcus ventriculi	5 (1.9%)
Intestinal metaplasia in stomach	4 (1.5%)
Duodeno-gastric reflux	45 (16.7%)
AVM in stomach	1 (0.15%)
Signs of portal hypertension in stomach	1 (0.15%)

Table 11: Pathologies detected in the stomach

	Gastritis	Polyp	Erosion	Gastric ulcer	Foveolar hyperplasia	Early malignancy
Seen by both	22	3	15	3	3	1
Seen by MCCE only	9	0	3	2	0	0
Seen by endoscopy only	0	0	2	0	0	0

Table 12: Gastroscopies performed due to MCCE findings and the results of their comparison

10. DISCUSSION

Data in the literature show that the distal section of the oesophagus, Z-line, cardia, fundus, corpus, angulus, antrum and pylorus can be visualised well and completely using the NaviCam capsule in more than 95% of patients (15). In an average case, exploration of the entire gastric lining takes 20 to 30 minutes. In 40 to 59% of the cases, the capsule can successfully be guided by magnetic control through the pylorus, which significantly reduces gastric transit time compared to conventional capsule endoscopy. As the total operation time of a NaviCam magnetic capsule endoscope is 10 to 12 hours depending on image recording speed, having surveyed the stomach, one capsule is able to explore the entire small intestinal mucosa as well. In addition, if the capsule camera in the bulbus is turned toward the pylorus capturing the descending duodenum, the Vater papilla can also be visualised, which is feasible in 30% of all magnetic assisted capsule endoscopy procedures (25).

NaviCam MCCE was compared with standard gastroscopy in two clinical trials of 68 and 350 patients, respectively, by Chinese investigators. In these trials, 91.2% and 93.4% of all mucosal abnormalities detected by gastroscopy were successfully identified by MCCE (26, 27). In patients with early-stage gastric cancer confirmed by gastroscopy, the NaviCam MCCE performed by an independent investigator prior to ESD successfully identified 9 out of 10 lesions (28), the only unidentified abnormality being a subcardial lesion smaller than 10 mm. In the past two years, a total of 3,182 asymptomatic patients aged over 50 years were screened for gastric cancer using NaviCam MCCE in 99 screening centres in China. In this symptom-free population, stomach cancer was diagnosed and screened in 0.78%, GIST in 3.6%, gastric ulcer in 4.9%, and benign gastric polyp in 10.4% of the patients before the appearance of symptoms. The investigators found that the technology improved not only patient adherence and compliance compared with biannually performed gastroscopic screening but could also detect a higher percentage of stomach cancers (total number of gastric cancer cases in all age groups, MCCE: 0.22% vs gastroscopy: 0.17%) (29).

An article published in July 2018 reviewing the literature on magnetic capsule endoscopy found that the average diagnostic accuracy for gastric diseases was over 90% (30). Quoting from a publication by recognised authors summarising trial results, magnetically controlled capsule endoscopy is a promising technique for visualisation of the stomach and may partially replace diagnostic gastroscopy in the near future. Achieving appropriate cleanliness of the stomach, procedure time, training of health professionals to perform the examinations, and cost-effectiveness are, however, still areas to be explored in the future (31).

The past few years have highlighted a particular advantage of capsule endoscopy: apart from its convenience, it also helps reduce the risk of infection transmission, a consideration especially important since the start of the COVID pandemic in 2019. Using a special remote-control system, the physician is able to perform MCCE from another room, even a distant one connected via the Internet. In our clinical study, we conducted 15 remote-controlled NaviCam examinations on the stomach with the operator staying in the same room with the patient for a total of 10 s, as opposed to the 35 min of a conventional examination, thus minimising the risk of infection transmission. Compared to the conventional modality, there was no difference in the diagnostic yield (32). Similarly, no difference was found between remote-controlled and conventional MCCEs in 40 patients in a randomised Chinese study in two centres, either in terms of feasibility or diagnostic yield, and no adverse events were reported (33). In another study, the same remote control was implemented via 5G from a different institute, and again no difference was found in the 20 patients in image quality, manoeuvrability, or visualisation of landmark anatomical sites (34).

Another benefit of magnetic steering is reduced transit time in the stomach, which, in case of delayed gastric transit, may facilitate the exploration of the entire small intestine during the operation time of the capsule. Furthermore, it may increase the Vater papilla visualisation rate. A study in 2019 reported significantly better results with MCCE compared to the controls, both in terms of gastric transit time and exploration of the entire small intestine. Visualisation of the entire small intestine was successful in 100% of the patients undergoing MCCE and 94.2% in the control group. Gastric transit time was 22.2 min vs 84.5 min by the conventional procedure, and there was no difference in diagnostic yield between the two groups. (35).

Visual confirmation of the presence of Helicobacter pylori with standard white light endoscopy (WLI) has a relatively low accuracy. Moreover, WLI endoscopy correlates poorly with histopathological findings of Helicobacter pylori induced gastritis. Recently, a retrospective study evaluated the potential advantage of a special electronic chromoendoscopy (linked colour imaging - LCI) technique capable of highlighting diffuse reddish areas in the mucosa, i.e. inflammatory regions in detecting Helicobacter. Compared to conventional WLI, LCI provided significantly higher accuracy and sensitivity in the 60 patients (30 Helicobacter positive, 30 negative) whose gastroscopic images were analysed by the investigators (36). In our study, we found no correlation between the HP status and the extent, type or severity of gastritis observed on MCCE.

Wide-spread use of MCCE in western countries may be hindered by differences in the prevalence of gastric and oesophageal diseases between the East and the West. In eastern countries today, MCCE is mostly used for the detection of malignant and premalignant gastric lesions, which are more prevalent in the East. However, the present technology opens the door to further new technologies: subsequent developments would allow the MCCE technology to be extended to other regions of the gastrointestinal tract, e.g. the esophagus, which may facilitate the exploration of the Z-line with the diagnosis of erosive reflux disease and Barrett’s metaplasia, allowing wider use of the technique in western countries. With second-generation MCCE, visualisation of the esophagus, Z-line and Vater papilla have improved, as reported by Jiang et al. Furthermore, significantly more images were taken of the oesophagus while gastric transit time was shortened by one-third and capsule operation time increased. The average gastric examination time was 10 min, which is close to the one needed for conventional gastroscopy (37).

Gastroscopy, the gold standard for gastric exploration, has several unquestionable advantages over capsule endoscopy (precise manoeuvring, option for histopathology sampling or therapeutic intervention, washing of contaminated areas). On the other hand, it is uncomfortable for patients, and therefore it is mostly performed under sedation, which carries definite procedure-related risks. MCCE, as a patient-friendly, non-invasive technique, might be an alternative for patients who refuse to undergo gastroscopy and may increase patients' adherence to screening. MCCE of the stomach was approved by the Chinese Food and Drug Administration for the following diagnostic indications: (1) as an alternative diagnostic tool for patients who refuse to undergo gastroscopy; (2) screening for gastric diseases; (3) screening for gastric cancer; (4) diagnosis of various gastrointestinal inflammations; (5) follow-up for diseases like gastric varices, gastric ulcer, atrophic gastritis, and polyps after surgical or endoscopic removal (19).

No studies similar to the one we conducted where the entire upper gastrointestinal tract, including the stomach and the small bowel, was explored with the same capsule endoscope during MCCE have been carried out in Europe and published in the literature. Denzer et al. published a blinded, prospective trial in two French centres using the Intromedic manually controlled MCCE. A total of 189 patients were enrolled, and both conventional and capsule examinations were performed. Lesions were defined as major (requiring biopsy or endoscopic intervention) or minor ones. Twenty-three major lesions were identified in 21 patients. In this group, the capsule accuracy was 90.5%, compared to gold-standard gastroscopy under sedation with propofol. In the remaining 168 patients with minor lesions, the capsule accuracy was 88.1%. All patients preferred MCCE over gastroscopy. (38).

Visibility and cleanliness of the gastric mucosa, as well as appropriate imaging of landmark areas are key factors in diagnostic accuracy. Scanning landmarks is the primary objective in both manual and automatic examinations. In an earlier study published as an abstract, we assessed performance in manual and automatic modes using disks attached to a plastic stomach model as part of the learning process. Performance improved on repeated examinations, confirming the learning curve. Mapping of the entire inner gastric surface took a significantly shorter time in the second examination. However, the time required for visualising all surface signs with the automatic protocol was reproducibly half of that of the manual mode (20). These findings suggest that MCCE may become automated and performed by specially trained operators (qualified endoscopy health professionals) in the future, reducing the workload on gastroenterologists and thus alleviating the shortage of specialists.

Minimising bubbles and mucoid secretion in the stomach is a common problem in conventional as well as capsule examinations. To improve visibility, we developed a unique preparation procedure with a combination of bicarbonate, Pronase B and simethicone combined with a patient body rotation technique for better distribution in the stomach. For further improvement, we also rotated our patients during the MCCE examination to mobilise remaining gastric secretions, thus increasing mucosal visibility (21). Application of prokinetics, like motilin agonist erythromycin, might also be an option in future studies to improve visibility and reduce gastric lake content (39).

An inherent limitation of our study was that gastroscopy and MCCE were performed only on a limited number of patients. However, several previous studies demonstrated excellent diagnostic value and high accuracy compared to gastroscopy. In a recent meta-analysis by Zhang et al., in which four studies with a total of 612 patients were included, the results of MCCE and gastroscopy were compared. MCCE demonstrated a pooled sensitivity and specificity of 91% and 90%, respectively (40). A meta-analysis in 2021 reviewed 7 studies involving a total of 916 patients and 745 gastric lesions. Mean examination time was 21.92±8.87 min and overall sensitivity was 87% [95% (CI), 84%-89%]. In subgroup analyses, sensitivity was found to be 82% (95% CI: 71%-89%) for gastric ulcer, 82% (95% CI: 76%-87%) for gastric polyp, and 95% (95% CI: 86%-98%) for gastric erosion (41). In 2022 we reported our own results with MCCE performed for dyspeptic complaints in a total of 270 patients. In the examinations, we also used real-time AI-based laser detection and characterisation software, which helped identify focal lesions on the gastric mucosa during MCCE and allowed closer and more detailed observation of such abnormalities by means of manual guidance. No abnormalities were detected in the upper gastrointestinal tract in 40 patients (14.8%), and only insignificant inflammation was seen in the stomach in 102 patients (37.8%). In the rest of the cases, the following pathologies were identified: 73 (27%) erosive reflux, 6 (2.2%) suspected Barrett's metaplasia, 76 (28.1%) erosive or active antral gastritis, 45 (16.7%) duodeno-gastric biliary reflux, 25 (9.2%) foveolar hyperplasia, 9 (3.3%) solitary gastric polyp, 6 (2.2%) inflammation of the gastric corpus, 5 (1.9%) gastric ulcer, 4 (1.5%) suspected intestinal metaplasia, 3 (1,1%) AVM, and one (0.3%) suspected early flat carcinoma. Gastroscopy was performed in 31 patients (11.5%) with significant lesions on the same day; the gastroscopy findings were nearly identical with those of MCCE (23).

The advantage of MCCE is that both the stomach and the small bowel can be explored in one session. A retrospective review of a total of 768 MCCE examinations published in 2022 found the ratio of complete and successful gastric and small bowel mappings to be 92.58%, and more than 90% of the gastric lining was visualised. Small bowel exploration was completed in 97.4% of the cases. Gastric transit time was significantly reduced with magnetic guidance (42).

Artificial intelligence (AI) is increasingly used in every field of health care. AI can make the evaluation of findings faster and more accurate while reducing the human resources requirement of interventions. Due to the huge number of negative images, evaluation of capsule endoscopy is particularly time-consuming: the number of still images taken during an average small bowel capsule examination is 35,000-50,000, which must be evaluated by the physician one by one as the pathology may be seen in just a few of them. As a result, the average CE evaluation time is 60 to 90 min. A specialist can effectively evaluate a maximum of two exams; after that, the risk of missed lesions greatly increases. Therefore, while capsule endoscopy is a patient-friendly, non-invasive procedure, with the evaluation techniques currently used, it can hardly be called doctor-friendly, which is clearly a major obstacle to its widespread use. Application of AI can reduce the time required for the procedure and consequently its cost and can also improve accessibility. The Ankon MCCE system is the first in the world to use a CE-licensed computer algorithm (ProScan) developed on an AI deep-learning network, which can separate images containing abnormalities from negative ones and select the former in small bowel capsule examinations, thus making evaluation easier. In a Chinese study in 2019 testing the efficacy of ProScan, Zhen Ding et al. presented the results achieved with a self-learning algorithm taught using 113 million images of 6,970 patients from 77 centres in the evaluation of small bowel capsule endoscopy images. 158,235 images from 1,970 patients were used to teach the convolutional neural network to distinguish between still images containing abnormalities and negative ones, then it was tested and validated on the imagery obtained in the small bowel capsule examinations of 5,000 patients. Finally, the results were compared with evaluations done by 20 gastroenterologists. The sensitivity and specificity achieved by the algorithm were 99.88% and 99.90%, respectively, while the sensitivity per lesion detection by the gastroenterologists was 74.57%; evaluation time was also significantly lowered by the algorithm (from 96 min to nearly 6 min) (43). Xia et al. presented a deep-learning algorithm taught by gastric capsule endoscopic images from 1 million MCCEs. Sensitivity and specificity for focal lesion identification in the stomach were found 96.2% and 76.2%, respectively. The images were characterised into 7 groups (erosion, polyp, ulcer, submucosal tumour, xanthoma, normal mucosa, non-evaluable image). The overall sensitivity for all lesions was nearly 90% (44). Publication of a large international, multi-centre, blinded, prospective study (ARTIC – ARTificial Intelligence Capsule endoscopy) is currently underway, which included the University of Szeged and the Endo-Kapszula Private Medical Centre among independent study sites. 137 anaemic patients with suspected small bowel bleeding who tested negative in previous gastro- and colonoscopies were enrolled. Small bowel capsule images were evaluated by independent groups of physicians with or without AI-based ProScan. The results of the interim analysis suggest that the use of ProScan significantly improved diagnostic sensitivity for P1 and P2 lesions per patient (Sorin classification) compared to conventional evaluation, and significantly lowered the ratio of missed P1+P2 lesions from 35% to 12%, while decreasing evaluation time from 34 min to 3.5 min (the ARTIC study submitted for publication).

In summary, review of the international literature, as well as our own results and experience with the new MCCE technique suggest that capsule endoscopy, already a gold standard in small bowel investigations, in the future may offer a non-invasive alternative in the diagnosis of upper gastrointestinal tract disorders, due to magnetic navigation, robotics, automated control, and fast evaluation made possible by the use of artificial intelligence. Naturally, further studies are needed to develop techniques by which optimal gastric cleanliness, maintenance of the capsule in the oesophagus and increased visualisation of the Z-line can be achieved. In addition, MCCE may become suitable for targeted biopsy in the near future, further reducing the ratio of patients requiring conventional panendoscopy following the capsule procedure.

11. CONCLUSIONS AND NEW RESULTS

Robotically guided and magnetically controlled capsule endoscopy is a promising non-invasive diagnostic method which may significantly improve the diagnostic yield of capsule endoscopic examinations in the endoscopically explorable sections of the gastrointestinal tract and as such may become a useful, non-invasive diagnostic tool for GI screening of asymptomatic patients.

NEW RESULTS:

1. MCCE has been shown to be a feasible and effective method for exploration of the gastric and entire small bowel mucosa in 93.7% of tested patients. The average total procedure time was 5 h 48 min 35 s (5 h 46 min 37 s / 5 h 50 min 18 s).

2. Our team was the first to confirm that MCCE can visualize the complete upper gastrointestinal tract in one setting. Furthermore, we described in detail the methodology and published the steps and precise technique of the MCCE procedure.

3. Helicobacter pylori positivity was confirmed by urea breath tests in 32.7% of patients tested for small bowel CE indication. No significant correlation was found between the Helicobacter status and the type (proximal or antral), distribution (diffuse or focal), or severity (minimal or active erosive) of gastritis.

4. MCCE is a safe and non-invasive procedure. Mild complications occurred in 4 patients (oesophageal and small bowel CE retention in two patients each); each case could be resolved endoscopically or by conservative medication. Severe complications requiring surgery or hospitalization did not occur.

5. *In vitro* experimets with MCCE on plastic stomach model we revealed a 97% to 100% inner surface visibility in 20 to 30 min using automated and manually guided protocols, which confirms that the MCCE technology is suitable for complete mapping of the gastric inner surface and mucosa, if provided appropriate cleanliness and distension of the stomach with water is achieved.

6. In *in vivo* studies, we proved an excellent average visibility of the gastric mucosa, in patients with optimal gastric cleansing, was 100%, 100% and 97% in the antrum, corpus

and fornix, respectively. Average visibility in the fundus, corpus and antrum ranged between 92.4-87.68%, 96.64-90.78% and 99.69-93.86%, respectively, due to the fact, that in some cases mucus and foam remaining in the gastric lake of the stomach.

7. Cleanliness and visibility of the gastric mucosa can be improved significantly by adding Pronase B and sodium bicarbonate to standard simethicone and 8-10 dl of clear water 30 minutes before the MCCE procedure.

8. If MCCEs conducted according to the modified oesophageal protocol first published by our team, the cardiac region and the Z-line could be partially and fully visualized in 90% and 73% of the patients, respectively, confirming feasibility of capsule endoscopic exploration of the distal oesophagus and the cardia.

9. With an active magnetic guidance of the capsule a transpyloric transit can be achieved within 30 min in 41.9% of the cases, and afterwards the Vater papilla can be fully visualized in 30% of patients.

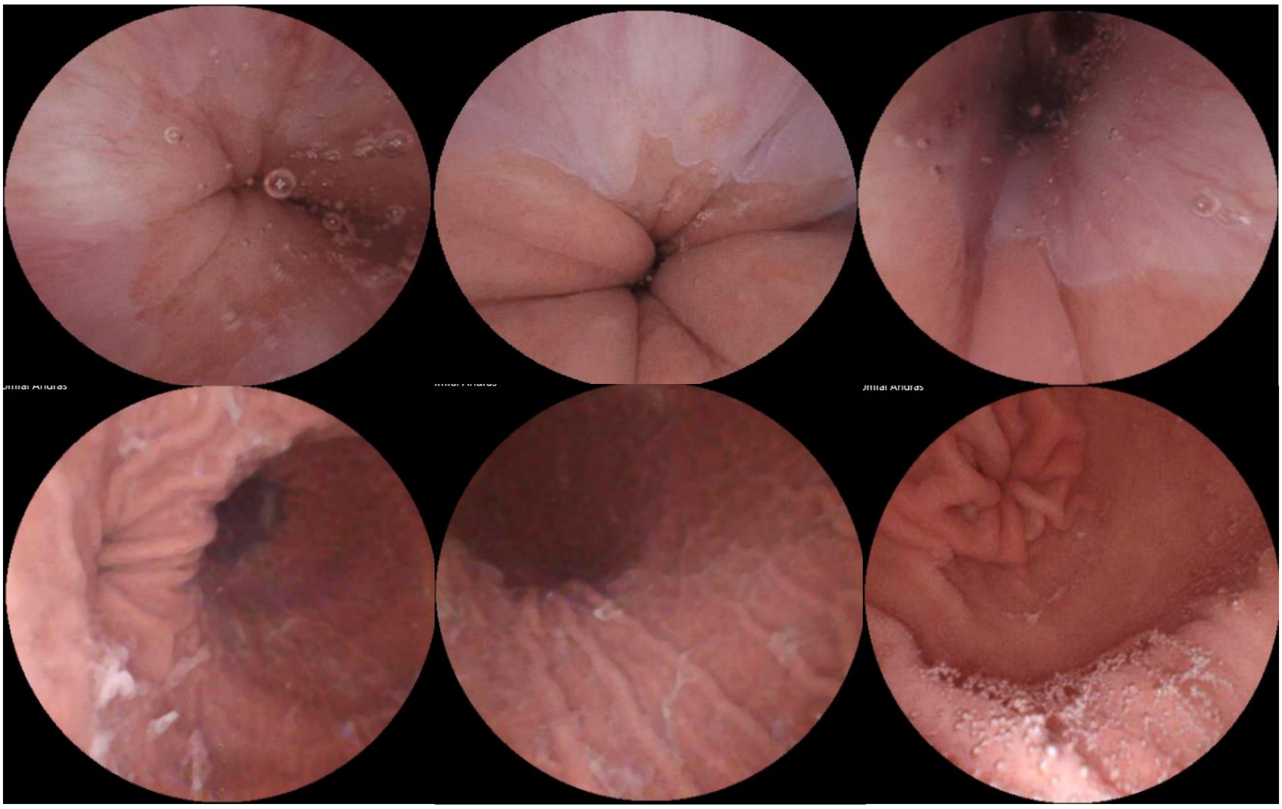
10. The diagnostic yield for detecting any abnormalities in the stomach and the small bowel with MCCE for small intestinal indication was 81.8%, 68.6% for minor and 13.3% for major pathologies. 25.8% of the abnormalities were found in the small bowel and 74.2% in the stomach. The diagnostic yield for stomach and small bowel pathologies was 4.9% and 8.4%, for major and 55.9% and 12.7%, respectively, for minor pathologies.

11. MCCE and gastroscopy findings were compared in 31 patients who underwent both procedures on the same day. The results demonstrated high concordance and similar diagnostic effectiveness in the detection of focal and diffuse lesions.

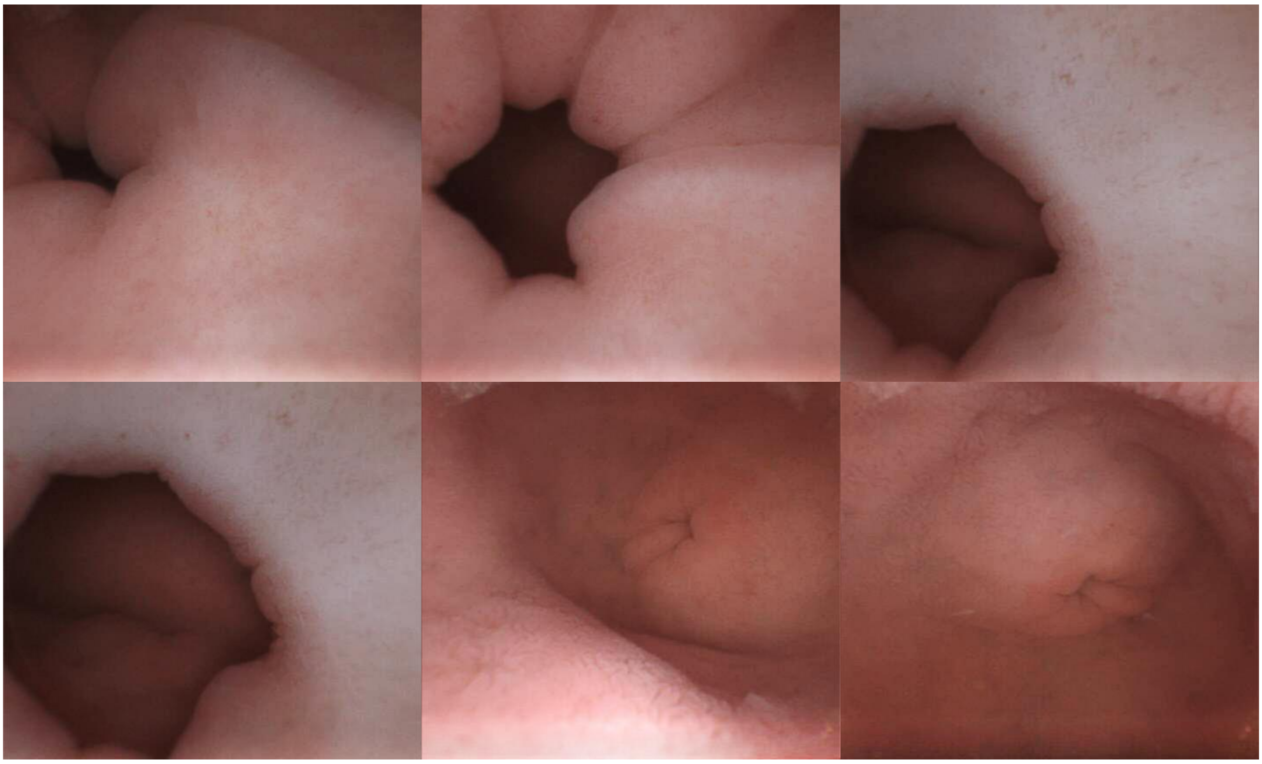
In conclusion, combined gastric and small bowel MCCE is recommended in patients referred for small bowel capsule endoscopy (IBD, OGIB and iron deficiency anaemia), as it significantly increases the diagnostic yield of the capsule procedure. Furthermore, in view of high MCCE accuracy compared to gastroscopy, particularly in focal lesions, gastric MCCE may be considered in patients under the age of 40 with complaints suggesting functional dyspepsia without alarm symptoms in whom gastroscopy is not justified, thus reducing the number of unnecessary and invasive gastroscopic examinations, and shortening the waiting list, without risking to miss any significant gastric lesions or pathologies.

12. PICTURES FROM OUR STUDIES

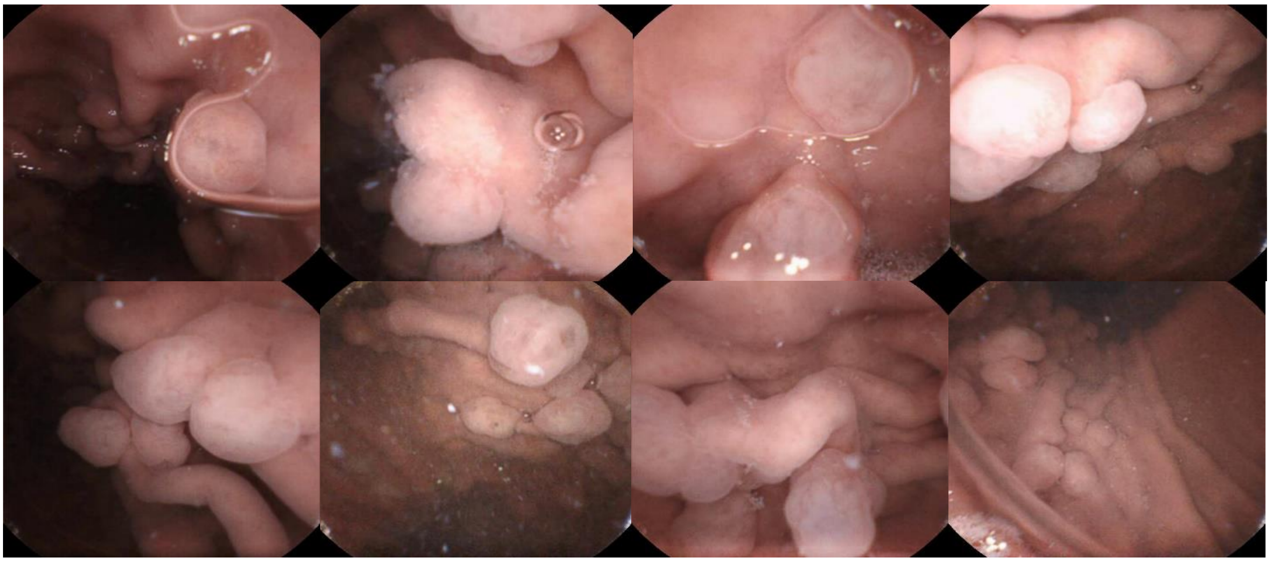
Picture 1: Negative images by MCCE; column 1: oesophagus, coloumns 2-4: stomach.



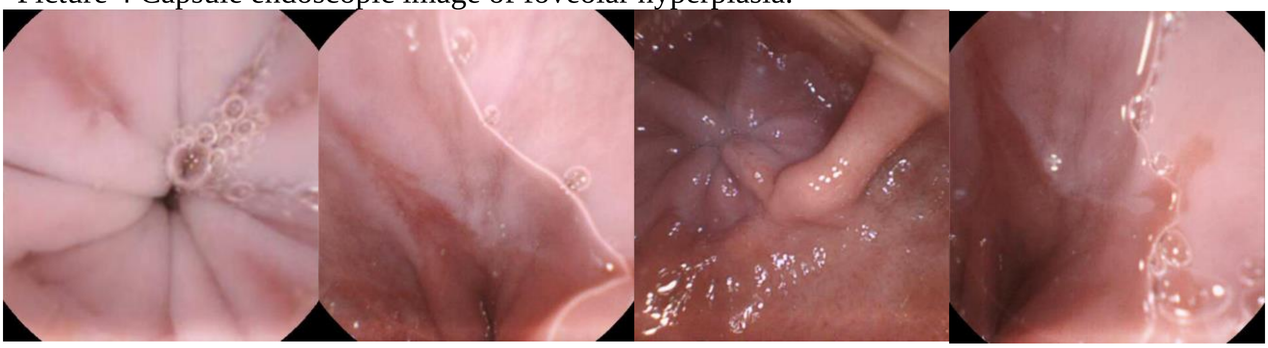
Picture 2: Upper row: oesophagus, Z-line; lower row from left to right: cardia, corpus and antrum by MCCE.



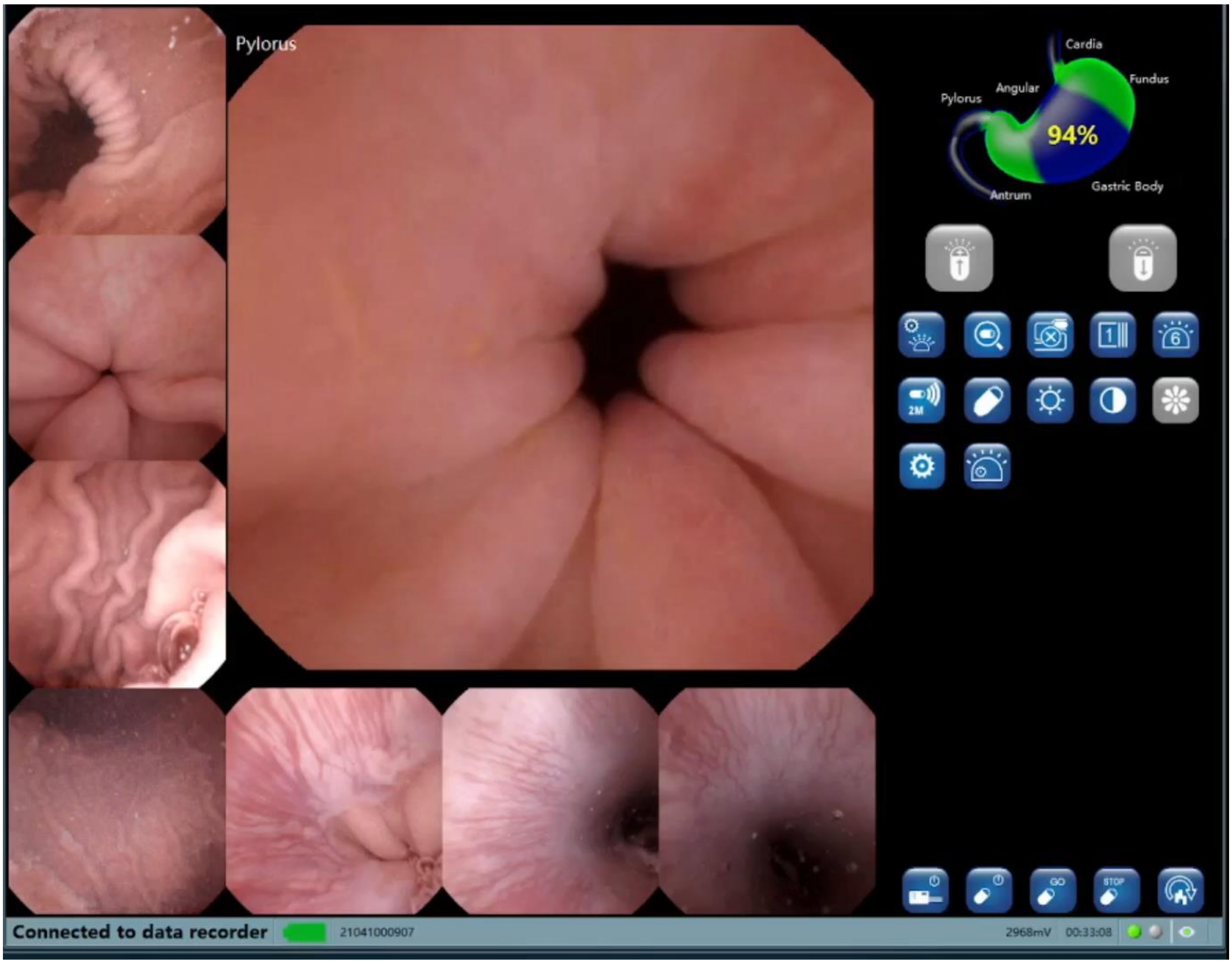
Picture 3: Image of pyloric ring and antrum taken during magnetically controlled transpyloric transit.



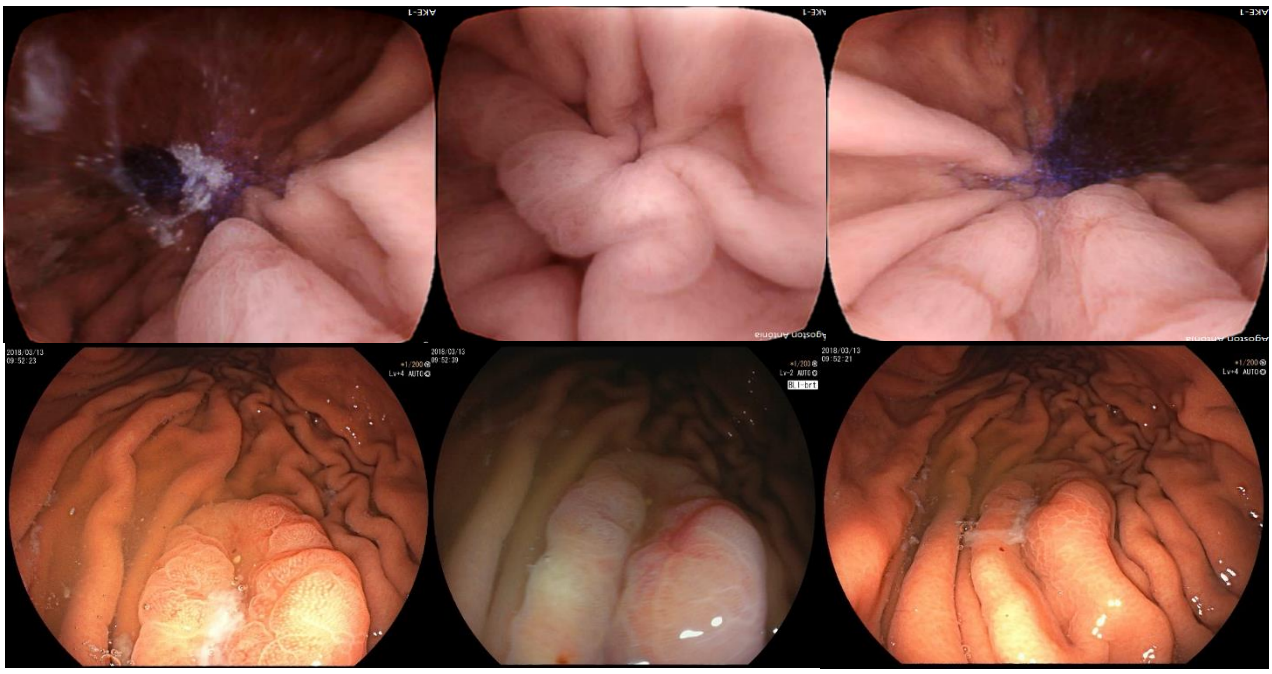
Picture 4 Capsule endoscopic image of foveolar hyperplasia.

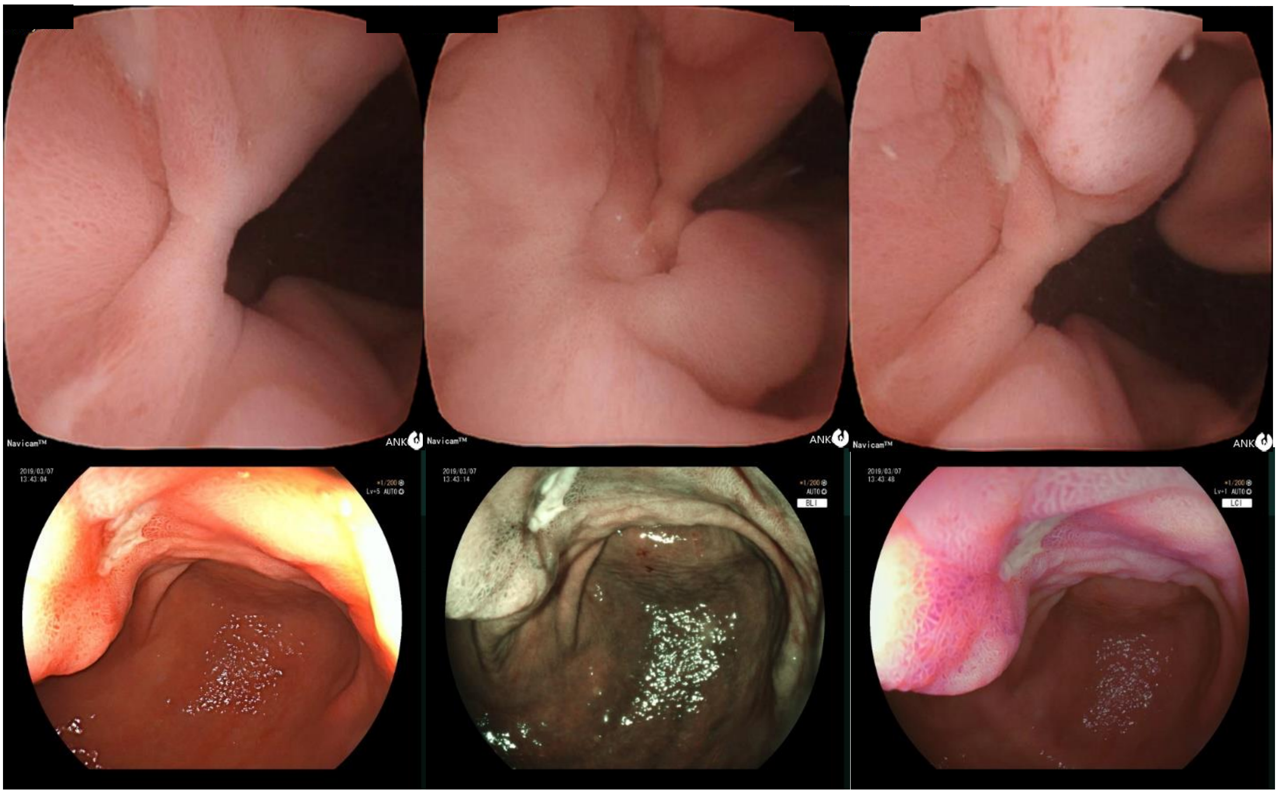


Picture 5: Capsule endoscopic image of erosive reflux and hiatus hernia.

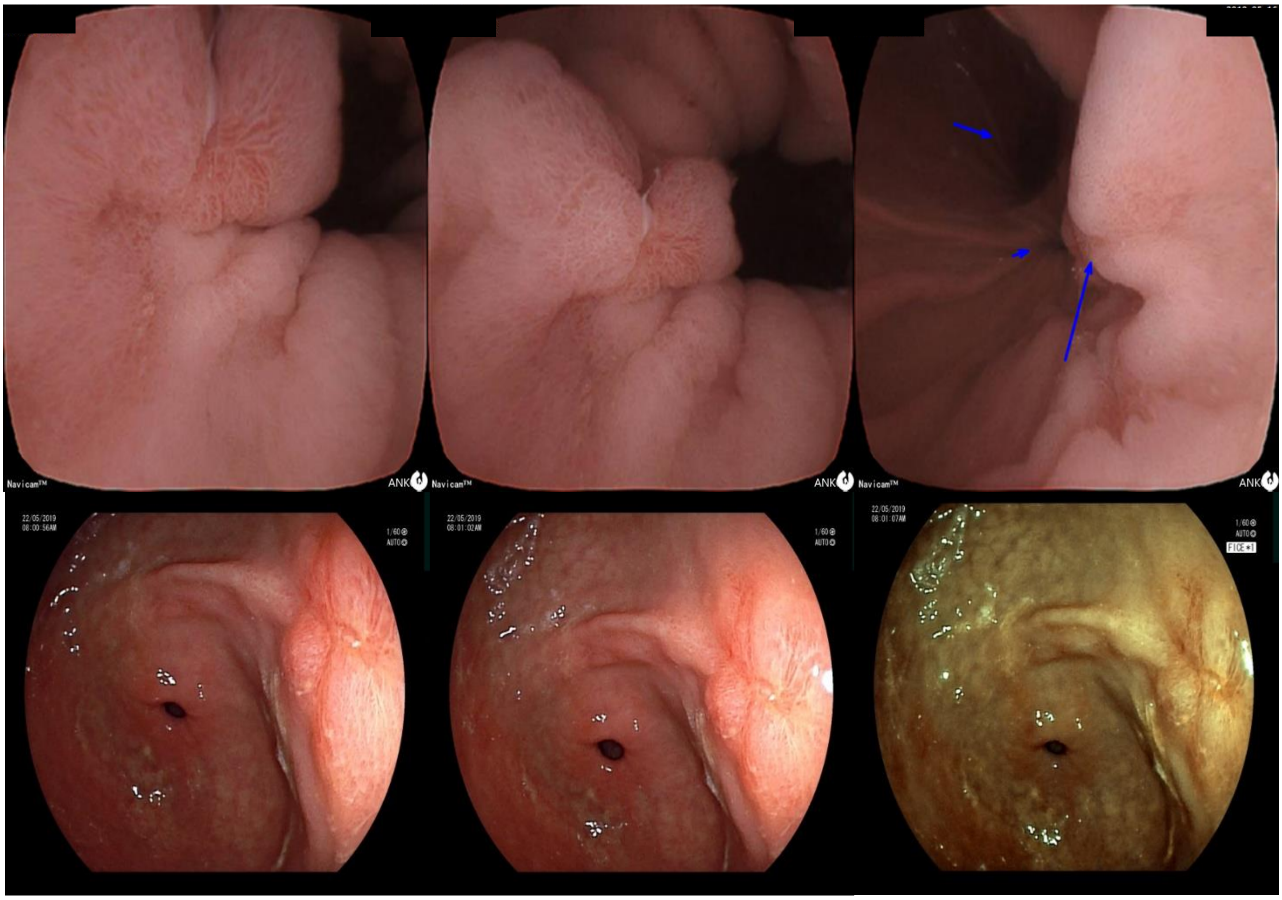


Picture 6: Real-time image viewing software during examination.


Picture 7: Endoscopic image of gastric B-cell lymphoma; upper row: capsule endoscopy, lower row: gastroscopy.



Picture 8: Image of gastric ulcer; upper row: MCCE, lower row: gastroscopy.



Picture 9: Image of gastric ulcer; upper row: MCCE, lower row: gastroscopy.

13. ACKNOWLEDGEMENTS

I wish to say thank you to all my colleagues, current and previous, for their assistance in gastroenterology, including my research in the field of capsule endoscopy. Fortunately, there are so many who have contributed to my research that it would be difficult to list each of them by name. Special thanks are due to my mentor, Professor István Rácz, who introduced me to gastroenterology; he is the one who got me acquainted with capsule endoscopy and started me on the bumpy road of scientific research. I am grateful to Dr Ádám Finta, Dr Krisztina Helle, Dr Barbara Lovász, Dr László Oczella, Dr Rebeka Liebe, and Dr András Rosztóczy, my workmates and members of our team, for their assistance in the current research and the publication of results. I thank the assistants for their professional help and support in carrying out the capsule endoscopy examinations, evaluating the results and creating a database. I am most grateful to my supervisor, Professor László Madácsy, who, despite the heavy workload of the daily routine, has supervised and assisted my research, steering me in the right direction.

I thank my parents for assisting and supporting me in my studies, paving the way to a career which has now resulted in the present paper. I am eternally grateful to my wife and children, who have supported and encouraged me all along, patiently enduring my absences and forgiving me for the hours I did not spend with them.

14. LIST OF ABBREVIATIONS

AI – artificial intelligence
AVM - arteriovenosus malformation
FAMCE - fully automated magnetically controlled capsule endoscopy
FDA – food and drug administration
GI - gastrointestinal
HD – high definition
H. pylori, HP - Helicobacter pylori
IBD – inflammatory bowel disease
LCI - linked color imaging
MACE – magnetically assisted capsule endoscopy
MCCE – magnetically controlled capsule endoscopy
CE – capsule endoscopy
MRI - magnetic resonance imaging
OGIB – obscure gastrointestinal bleeding
PEG - polyethylene glycol
PPI – proton pump inhibitor
SD – standard deviation
UBT - urea breathing test
WLI – white light endoscopy

15. REFERENCES

1. Iddan G, Meron G, Glukhovsky A, et al. Wireless capsule endoscopy. Nature 2000; 455: 417–8.
2. Adler SN. The history of time for capsule endoscopy. Ann Transl Med 2017; 5(9): 194.
3. Goenka MK, Majumder S, Goenka U. Capsule endoscopy: Present status and future expectation. World J Gastroenterol 2014; 20(29): 10024–10037.
4. Rondonotti E, Spada C, Adler S, et al. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Technical Review. Endoscopy 2018; 50(4): 423–446.
5. Eliakim R, Yassin K, Shlomi I, et al. A novel diagnostic tool for detecting oesophagealpathology: the PillCam oesophageal video capsule. Aliment Pharmacol Ther 2004; 20: 1083–89.
6. Eliakim R, Fireman Z, Gralnek IM, et al. Evaluation of the PillCam Colon capsule in the detection of colonic pathology: results of the first multicenter, prospective, comparative study. Endoscopy. 2006; 38: 963–70.
7. Nouda S1, Ota K1, Higuchi K1. Retrograde colon capsule endoscopy with the self-propelling capsule endoscope: The first human trial (with videos). 2018 Jan; 30(1): 117–118. doi: 10.1111/den.12969 Epub 2017 Oct 17.
8. Swain P, Toor A, Volke F, Keller J, Gerber J, Rabinovitz E, Rothstein RI. Remote magnetic manipulation of a wireless capsule endoscope in the esophagus and stomach of humans (with videos). Gastrointest Endosc. 2010 Jun;71(7):1290-3. doi: 10.1016/j.gie.2010.01.064. Epub 2010 Apr 24. PMID: 20417507.
9. Rey JF, Ogata H, Hosoe N, et al. Inspection of the human stomach using remote-controlled capsule endoscopy: a feasibility study in healthy volunteers (with videos). Gastrointest Endosc 2011. Jan; 73(1): 22–8.
10. Rey JF, Ogata H, Hosoe N, Ohtsuka K, Ogata N, Ikeda K, Aihara H, Pangtay I, Hibi T, Kudo SE, Tajiri H. Blinded nonrandomized comparative study of gastric examination with a magnetically guided capsule endoscope and standard

videoendoscope. Gastrointest Endosc. 2012 Feb.; 75(2):373-81. doi: 10.1016/j.gie.2011.09.030. Epub 2011 Dec 9. PMID: 22154417.

11. Imdadur Rahman, Mathieu Pioche, Chan Sup Shim. Magnet Assisted Capsule Endoscopy (MACE) in the Upper GI Tract Is Feasible: First Human Series Using the Novel Mirocam-Navi System. GIE 2014 May; 79(5S): AB122.

12. Gu H, Zheng H, Cui X, et al. Maneuverability and safety of a magnetic-controlled capsule endoscopy system to examine the human colon under real-time monitoring by colonoscopy: a pilot study. Gastrointestinal Endoscopy 2017; 85(2): 438–443. doi: 10.1016/j.gie.2016.07.053 Epub 2016 Jul 29

13. Ching HL, Hale MF, Kurien M, et al. Diagnostic yield of magnetically assisted capsule endoscopy versus gastroscopy in recurrent and refractory iron deficiency anemia. Endoscopy 2018 Oct 25. doi: 10.1055/a-0750-5682 Epub ahead of print.

14. Ciuti G, Donlin R, Valdastri P, Arezzo A, Menciassi A, Morino M, Dario P. Robotic versus manual control in magnetic steering of an endoscopic capsule. Endoscopy. 2010 Feb; 42(2):148-52. doi: 10.1055/s-0029-1243808. Epub 2009 Dec 16. PMID: 20017088.

15. Liao Z, Duan XD, Xin L et al. Feasibility and safety of magnetic-controlled capsule endoscopy system in examination of human stomach: a pilot study in healthy volunteers. J Interv Gastroenterol 2012 Oct-Dec; 2(4): 155–160. doi: 10.4161/jig.23751 Epub 2012 Oct 1.

16. Jiang X, Pan J, Li ZS, Liao Z. Standardized examination procedure of magnetically controlled capsule endoscopy. VideoGIE. 2019 May 30;4(6):239-243. doi: 10.1016/j.vgie.2019.03.003. PMID: 31194028; PMCID: PMC6545453.

17. Zhang Y, Zhang Y, Huang X. Development and Application of Magnetically Controlled Capsule Endoscopy in Detecting Gastric Lesions. Gastroenterol Res Pract. 2021 Dec 30; 2021:2716559. doi: 10.1155/2021/2716559. PMID: 35003252; PMCID: PMC8739542

18. Geropoulos G, Aquilina J, Kakos C, Anestiadou E, Giannis D. Magnetically Controlled Capsule Endoscopy Versus Conventional Gastroscopy: A Systematic Review and Meta-Analysis. J Clin Gastroenterol. 2021 Aug 1;55(7):577-585. doi: 10.1097/MCG.0000000000001540. PMID: 33883514.

19. Chinese Digestive Endoscopist Committee; Chinese Endoscopist Association, the Health Management and Physical Examination Committee of Digestive Endoscopy; Capsule Endoscopy Collaboration Group of Chinese Society of Digestive Endoscopy; Chinese Anti-Cancer Association, the Society of Oncological Endoscopy; Chinese Society of Health Management. [The China expert consensus of clinical practice for magnetically controlled capsule gastroscopy (2017, Shanghai)]. Zhonghua Nei Ke Za Zhi. 2017 Nov 1;56(11):876-884. Chinese. doi: 10.3760/cma.j.issn.0578-1426.2017.11.023. PMID: 29136725.

20. Szalai M, Oczella L, Lovasz BD, Madacsy L. Surface mapping in plastic gastric model assisted by a robotic autoscan program with a new magnetically controlled gastric capsule endoscopy system compared to manual controlling. United European Gastroenterol J. 2018:415–A415.

21. Schmiedt P, Szalai M, Oczella L, Zsobrak K, Lovasz BD, Dubravcsik Z, Madacsy L. A new preparation method for improving gastric mucosal visibility and cleanliness during magnetically assisted capsule endoscopy: A prospective study. Endoscopy 2019; 51: S7

22. Szalai, Milán; Helle, Krisztina; Lovász, Barbara Dorottya; Finta, Ádám; Rosztóczy, András; Oczella, László; Madácsy, László First prospective European study for the feasibility and safety of magnetically controlled capsule endoscopy in gastric mucosal abnormalities WORLD JOURNAL OF GASTROENTEROLOGY 28: 20 pp. 2227-2242., 16 p. (2022)

23. Lovasz B., Finta A., Szalai M., Helle K., Oczella L., Rosztoczy A., Madacsy L. Results with magnetically controlled capsule endoscopy combined with real-time AI-lesion detection in patients with uninvestigated dyspepsia: a prospectiv study Central European Journal of Gastroenterology and Hepatology Volume 8, Supplementum 1 / June 2022 pp 89-90

24. Finta, A; Lovász, BD; Szalai, M; Oczella, L; Dubravcsik, Z; Madácsy, L Our New Experiences with a Roboticcally Controlled Magnetic Capsule Endoscopy System to Evaluate Esophageal and Gastric Disoders in Patients Referred For Small Bowel Capsule Endoscopy ENDOSCOPY 53: S 01 pp. 97-97., 1 p. (2020) DOI32868127

25. Jiang X, Qian YY, Liu X, et al. Impact of magnetic steering on gastric transit time of a capsule endoscopy (with video). Gastrointest Endosc 2018 Oct; 88(4): 746–754. doi: 10.1016/j.gie.2018.06.031 Epub 2018 Jul 11.

26. Zou WB, Hou XH, Xin L, et al. Magnetic-controlled capsule endoscopy vs. gastroscopy for gastric diseases: a two-center self-controlled comparative trial. Endoscopy 2015 Jun; 47(6): 525–8. doi: 10.1055/s-0034-1391123 Epub 2015 Jan 15.

27. Zhuan L, Xi H, En-Qiang LH, et al. Accuracy of Magnetically Controlled Capsule Endoscopy, Compared With Conventional Gastroscopy, in Detection of Gastric Diseases. Clinical Gastroenterology and Hepatology 2016; 14: 1266–1273.

28. Qian YY, Zhu SG, Hou X, et al. Preliminary study of magnetically controlled capsule gastroscopy for diagnosing superficial gastric neoplasia. Dig Liver Dis 2018 Oct; 50(10): 1041–1046. doi: 10.1016/j.dld.2018.04.013 Epub 2018 Apr 24.

29. Zhao AJ, Qian YY, Sun H, et al. Screening for gastric cancer with magnetically controlled capsule gastroscopy in asymptomatic individuals. Gastrointest Endosc 2018 Sep; 88(3): 466–474.e1. doi: 10.1016/j.gie.2018.05.003 Epub 2018 May 9.

30. Nam SJ1, Lee HS2, Lim YJ3. Evaluation of Gastric Disease with Capsule Endoscopy. Clin Endosc 2018 Jul; 51(4): 323–328. doi: 10.5946/ce.2018.092 Epub 2018 Jul 31.

31. Spada C1, Hassan C2, Costamagna G3. Magnetically controlled capsule endoscopy for the evaluation of the stomach. Are we ready for this? Dig Liver Dis 2018 Oct; 50(10): 1047–1048. doi: 10.1016/j.dld.2018.07.039 Epub 2018 Aug 7.

32. Finta, A.; Helle, K.; Szalai, M.; Madacsy, L. Use of Magnetically Controlled Capsule Endoscopy by Remote-Control During Pandemic ENDOSCOPY 54: S 01 pp. 261-261., 1 p. (2022)

33. Zhu JH, Pan J, Xu XN, Liu YW, Qian YY, Jiang X, Jiang B, Zhou W, Linghu EQ, Li ZS, Liao Z. Noncontact magnetically controlled capsule endoscopy for infection-free gastric examination during the COVID-19 pandemic: a pilot, open-label, randomized trial. Endosc Int Open. 2022 Feb 15;10(2): E163-E170. doi: 10.1055/a-1648-2238. Erratum in: Endosc Int Open. 2022 Mar 17;10(2):C2. PMID: 35178334; PMCID: PMC8847063.

34. Zhang T, Chen YZ, Jiang X, He C, Pan J, Zhou W, Hu JP, Liao Z, Li ZS. 5G-based remote magnetically controlled capsule endoscopy for examination of the stomach and

small bowel. United European Gastroenterol J. 2022 Nov 23. doi: 10.1002/ueg2.12339. Epub ahead of print. PMID: 36416805.

35. Luo YY, Pan J, Chen YZ, Jiang X, Zou WB, Qian YY, Zhou W, Liu X, Li ZS, Liao Z. Magnetic Steering of Capsule Endoscopy Improves Small Bowel Capsule Endoscopy Completion Rate. Dig Dis Sci. 2019 Jul;64(7):1908-1915. doi: 10.1007/s10620-019-5479-z. Epub 2019 Feb 6. PMID: 30725289.

36. Dohi O, Yagi N, Onozawa Y, Kimura-Tsuchiya R, Majima A, Kitaichi T, Horii Y, Suzuki K, Tomie A, Okayama T, Yoshida N, Kamada K, Katada K, Uchiyama K, Ishikawa T, Takagi T, Handa O, Konishi H, Naito Y, Itoh Y. Linked color imaging improves endoscopic diagnosis of active Helicobacter pylori infection. Endosc Int Open. 2016 Jul;4(7): E800-5. doi: 10.1055/s-0042-109049. PMID: 27556101; PMCID: PMC4993904.

37. Jiang B, Qian YY, Pan J, Jiang X, Wang YC, Zhu JH, Zou WB, Zhou W, Li ZS, Liao Z. Second-generation magnetically controlled capsule gastroscopy with improved image resolution and frame rate: a randomized controlled clinical trial (with video). Gastrointest Endosc. 2020 Jun;91(6):1379-1387. doi: 10.1016/j.gie.2020.01.027. Epub 2020 Jan 22. PMID: 31981648.

38. Denzer UW, Rösch T, Hoytat B, Abdel-Hamid M, Hebuterne X, Vanbiervielt G, Filippi J, Ogata H, Hosoe N, Ohtsuka K, Ogata N, Ikeda K, Aihara H, Kudo SE, Tajiri H, Treszl A, Wegscheider K, Greff M, Rey JF. Magnetically guided capsule versus conventional gastroscopy for upper abdominal complaints: a prospective blinded study. J Clin Gastroenterol. 2015 Feb; 49(2):101-7. doi: 10.1097/MCG.0000000000000110. PMID: 24618504.

39. Niv E, Bonger I, Barkay O, Halpern Z, Mahajna E, Depsames R, Kopelman Y, Fireman Z. Effect of erythromycin on image quality and transit time of capsule endoscopy: a two-center study. World J Gastroenterol. 2008 Apr 28;14(16):2561-5. doi: 10.3748/wjg.14.2561. PMID: 18442206; PMCID: PMC2708370.

40. Zhang, H., Chen, J., Li, J., Huang, C., Li, M., Wu, W., & Jiang, J. (2020). Use of magnetically controlled capsule endoscopy for the diagnosis of gastric diseases in adults: a systematic review and meta analysis. *Digestive Medicine Research*. 2020; 3: 42. doi: 10.21037/dmr-20-14

41. Geropoulos G, Aquilina J, Kakos C, Anestiadou E, Giannis D. Magnetically Controlled Capsule Endoscopy Versus Conventional Gastroscopy: A Systematic Review and Meta-Analysis. J Clin Gastroenterol. 2021 Aug 1;55(7):577-585. doi: 10.1097/MCG.0000000000001540. PMID: 33883514.

42. Liu YW, Wang YC, Zhu JH, Jiang X, Zhou W, Zhang J, Liao Z, Linghu EQ. Magnetically controlled capsule endoscopy in one-time gastro-small intestinal joint examination: a two-centre experience. BMC Gastroenterol. 2022 May 4;22(1):222. doi: 10.1186/s12876-022-02302-0. PMID: 35509022; PMCID: PMC9069740.

43. Ding Z, Shi H, Zhang H, Meng L, Fan M, Han C, Zhang K, Ming F, Xie X, Liu H, Liu J, Lin R, Hou X. Gastroenterologist-Level Identification of Small-Bowel Diseases and Normal Variants by Capsule Endoscopy Using a Deep-Learning Model. Gastroenterology. 2019 Oct;157(4):1044-1054.e5. doi: 10.1053/j.gastro.2019.06.025. Epub 2019 Jun 25. PMID: 31251929.

44. Xia J, Xia T, Pan J, Gao F, Wang S, Qian YY, Wang H, Zhao J, Jiang X, Zou WB, Wang YC, Zhou W, Li ZS, Liao Z. Use of artificial intelligence for detection of gastric lesions by magnetically controlled capsule endoscopy. Gastrointest Endosc. 2021 Jan; 93(1):133-139.e4. doi: 10.1016/j.gie.2020.05.027. Epub 2020 May 26. PMID: 32470426.

16. TABLES